Needles on the couch

Peggy Bosch

Acupuncture in the Treatment of Depression, Schizophrenia and Sleep Disorders

DONDERS

series

NEEDLES ON THE COUCH

Acupuncture in the Treatment of Depression, Schizophrenia and Sleep Disorders

Margaretha Petronella Carolina (Peggy) Bosch

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NEEDLES ON THE COUCH

Acupuncture in the Treatment of Depression, Schizophrenia and Sleep Disorders

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Chapter 1

General Introduction

The roots of education are bitter, but the fruit is sweet.

Aristotle

Psychiatry

At the start of a treatment in a psychiatric clinic, some patients expect to lie on a couch. Everyday practice in psychiatry in the 21st century, however, has little to do with the former concept that started with the work of Sigmund Freud, in which patients used to lie on the therapist's couch several times a week. In a psychiatric clinic nowadays, patients are treated by a multidisciplinary team with medication and psychotherapy of some kind. As to the effectiveness of treatment, Jensen (1990) found that patients were not very content with their treatment, and various reasons have been given to explain that (Astin, 1998); for example, conventional treatment has been ineffective (Jensen, 1990), has produced adverse effects (Jensen, 1990), or is seen as being too impersonal, too technologically oriented, and/or too costly (Astin, 1998). Studies show that patients tend to look for add-on complementary treatments (Samuels, Gropp, Singer, & Oberbaum, 2008). Particularly chronic patients, who suffer from an illness for a long time, often try complementary and alternative medicine (CAM) treatments in addition to allopathic medicine (Bhalerao et al., 2013; Metcalfe, Williams, McChesney, Patten, & Jetté, 2010; Rosenberg et al., 2008). From a Traditional Chinese Medicine point of view (Dey, 1999), patients with schizophrenia are like any other patients in that they have some disharmony in their bodies that need to be treated. Acupuncture can be used for such a treatment. An integrative form of treatment that includes acupuncture can be found in regular psychiatric practice in Asia. From personal clinical experience, most patients instantly report a better sleep after acupuncture; therefore, sleep might be a mediating factor in acupuncture treatment, which is the reason for the focus on sleep in the current Ph.D. research. Therefore, along with the treatment for patients with schizophrenia, came the treatment for patients with depression, who are also treated with acupuncture in China and Korea and who are often characterized by comorbid sleep disorders. Before describing the research questions in this Ph.D. thesis in more depth, I will first describe the population on which this research was conducted, and I will provide some important factors that played some roles in the lives of those patients. Finally, I will give a short overview of the theories behind acupuncture.

Schizophrenia

The worldwide prevalence of schizophrenia is estimated to be between 0.5% and 1%. The age of onset among men is usually earlier (about 21 years of age) than it is among women (27 years of age). When patients who have previously been diagnosed with schizophrenia turn 30, about 90% of the men, but only 20% of the women, will present with a chronic stage of the disease (Andreasen & Black, 2006).

For the clinical diagnosis of the disorder both the ICD-10 (10^{th} revision of the International Classification of Diseases and Related Health Problems) (World Health Organization, 1992) and the DSM-5 (The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) (American Psychiatric Association, 2013) can be used. Both systems are revised from time to time, and the next edition of the ICD is expected in 2015. Some large changes in the

diagnostic criteria of schizophrenia occurred in the transition from DSM-IV to DSM-V. Moreover, differences between the ICD and the DSM systems are apparent. An overview of the ICD and the DSM classifications of schizophrenia and of depression and sleep disorders are presented below in order to best describe the population at risk.

The characteristics for schizophrenia (F20), as described by the ICD-10, are presented in Table 1a). In addition schizophrenia can be divided into the following subtypes: paranoid schizophrenia, disorganized schizophrenia, catatonic schizophrenia, undifferentiated schizophrenia, residual schizophrenia, other schizophrenia, and schizophrenia unspecified (World Health Organization, 1992).

Table 1a.

According to the ICD-10 (World Health Organization, 1992), the following symptoms are characteristic for schizophrenia.

1. At least one of the following must be present:
   - thought echo, thought insertion or withdrawal, or thought broadcasting;
   - delusions of control, influence, or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations; delusional perception;
   - hallucinatory voices giving a running commentary on the patient's behavior, or discussing the patient among themselves, or other types of hallucinatory voices coming from some part of the body;
   - persistent delusions of other kinds that are culturally inappropriate and completely impossible (e.g., being able to control the weather, or being in communication with aliens from another world).
2. *Or* at least two of the following:
   - persistent hallucinations in any modality, when occurring every day for at least 1 month, when accompanied by delusions (which may be fleeting or half-formed) without clear affective content, or when accompanied by persistent overvalued ideas;
   - neologisms, breaks, or interpolations in the train of thought, resulting in incoherence or irrelevant speech;
   - catatonic behavior, such as excitement, posturing or waxy flexibility, negativism, mutism, and stupor;
   - negative symptoms, such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses (it must be clear that these are not due to depression or to neuroleptic medication).

G2. Most commonly used exclusion clauses:

1. If the patient also meets criteria for manic episode or depressive episode, the criteria listed under G1(1) and G1(2) above must have been met *before* the disturbance of mood developed.
2. The disorder is not attributable to organic brain disease or to alcohol- or drug-related intoxication, dependence, or withdrawal.

Note. G means General criteria that must be fulfilled by all members of a group of disorders.

According to the DSM-5 (American Psychiatric Association, 2013), schizophrenia may be diagnosed when a patient has at least two of the following symptoms at the same time (see

Table 1b) for at least a month (Tandon et al., 2013). Note that although the DSM-V eliminates the use of subtypes, the clinical studies of the present Ph.D. thesis were conducted in Germany, where the ICD-10 is used.

Table 1b.

According to the DSM-5 (American Psychiatric Association, 2013), the following symptoms are characteristic of schizophrenia.

- Delusions
- Hallucinations
- Disorganized speech
- Disorganized or catatonic behavior
- Negative symptoms

Patients with schizophrenia often differ in their signs and symptoms, but the following classification, according to the National Institute of Mental Health (2009), can be made:
1) Positive symptoms → these are symptoms that patients with schizophrenia have, but individuals without schizophrenia do not (Rosen et al., 1984). Here, one can think of delusions (Van Oosterhout et al., 2014).
2) Negative symptoms → these are elements that patients with schizophrenia no longer have, but individuals without schizophrenia do (Rosen et al., 1984). An example of a negative symptom in a patient with schizophrenia is, for instance, the blunted affect (Lee, Chun, Yoon, Park, & Kim, 2014).
3) Cognitive symptoms → like negative symptoms, cognitive symptoms (Buchanan et al., 2007) are subtle and are often not easy to recognize as part of the disorder. Here, one can think of working memory problems in individuals with schizophrenia (Mayer, Fukuda, Vogel, & Park, 2012).

The group of patients with schizophrenia is prone to suicide attempts. About one-third will conduct a suicide attempt; eventually about one in ten will succeed (Andreasen & Black, 2006). The global costs of schizophrenia for society are high (Knapp, Mangalore, & Simon, 2004; Goeree et al., 2005). Recently, a large German study by Frey (2014) was conducted on 8224 matched (schizophrenia patient versus healthy control) pairs. The costs per year as a result of schizophrenia were found to be 11.304 Euros per patient from the payers' perspective and 20.609 Euros from the German societal perspective. In addition, large variations among age groups were found. On the one hand, the highest direct medical costs were for the patients above 65 years of age whereas, on the other hand, the largest non-

medical costs were incurred by patients with schizophrenia who were under 25 years of age. The total cost due to schizophrenia as seen from the German societal perspective ranges between 9.63 billion Euros and 13.52 billion Euros. In the first year after the onset of the disease, costs are particularly great, and they stay relatively high up until the third year after onset (Nicholl, Akhras, Diels, & Schadrack, 2010).

Depression

In 2004, unipolar depression was listed by the World Health Organization (World Health Organization, 2008) as the third most important cause of disease burden worldwide, and a difference existed between low-income countries, for which unipolar depression was in eighth place, and middle- and high-income countries, for which it was in the first place. As can be seen in Table 2a, the ICD-10 (World Health Organization, 1992) uses a list of ten depressive symptoms to identify if someone suffers from depression and to determine the degree of depression. Depression is listed under F32 (depressive episode) and F33 (recurrent depressive disorder).

Table 2a.

According to the ICD-10 (World Health Organization, 1992), the following symptoms are characteristic of a major depressive disorder.

<u>At least one of these, most days, most of the time for at least 2 weeks:</u>

- Persistent sadness or low mood; and/or
- Loss of interest or pleasure
- Fatigue or low energy

<u>If any of above present, ask about associated symptoms:</u>

- Disturbed sleep
- Poor concentration or indecisiveness
- Low self-confidence
- Poor or increased appetite
- Suicidal thoughts or acts
- Agitation or slowing of movements
- Guilt or self-blame

A differentiation in the severity of depression can be made by using the following four subcategories: not depressed (< four symptoms), mild depression (four symptoms),

moderate depression (five to six symptoms), and severe depression (seven or more symptoms, with or without psychotic symptoms). According to the ICD-10, the depressive symptoms should exist for a duration of one month or longer, and every symptom should be present for most of every day (World Health Organization, 1992). According to the DSM-5 (American Psychiatric Association, 2013), depression occurs when the individual has at least five of the symptoms shown in Table 2b at the same time.

Table 2b.

According to the DSM-5 (American Psychiatric Association, 2013), the following symptoms are characteristic for major depressive disorder.

- A depressed mood during most of the day, particularly in the morning
- Fatigue or loss of energy almost every day
- Feelings of worthlessness or guilt almost every day
- Impaired concentration, indecisiveness
- Insomnia (an inability to sleep) or hypersomnia (excessive sleeping) almost every day
- Markedly diminished interest or pleasure in almost all activities nearly every day
- Recurring thoughts of death or suicide (not just fearing death)
- A sense of restlessness or being slowed down
- Significant weight loss or weight gain

Kessler, Chiu, Demler, Merikangas, and Walters (2005) conducted a survey on 9282 participants 18 years of age and older, and found that in 2004, 6.7% of U.S. adults experienced a major depressive episode. As for gender differences, women were found to have a higher prevalence (11.7%) than men (5.7%) (Ford & Erlinger, 2004).

Differences in the major depression and the suicide attempt rates across ethnic groups have been reported (Oquendo, Ellis, Greenwald, Malone, Weissman, & Mann, 2001). For instance, Oquendo, Lizardi, Greenwald, Weissman, and Mann (2004) found ethnic differences in the percentages of the American population that suffer from a major depression: 6.52% among whites, 4.57% among blacks, and 5.17% among Hispanics. However, one must keep in mind that factors such as the impact of the migration process and the socioeconomic status may account for, or at least have some impact on, these ethnic differences (Oquendo et al., 2004).

Psychiatric Population

Several diagnostic tools are used to describe patients and patient groups. For patients with schizophrenia, different outcomes where found in several studies (e.g., Ketter, Wang, Becker, Nowakowska, & Yang, 2004; Tsuang, Lyons, & Faraone, 1990). Those different outcomes can be explained by the extreme heterogeneity of the patient group studied (Buchanan & Carpenter, 1994). Not only might the different subtypes of schizophrenia be part of the explanation (Tsuang et al., 1990), but factors of chronicity might also be responsible for the different outcomes between studies (Liddle, Barnes, Morris, & Haque, 1989). Patients might function and feel differently in the first five years after having been diagnosed with a psychiatric disorder than in the years that follow. The same problem of clinical heterogeneity was found for depression (Goldberg, 2011; Ostergaard, Jensen, & Bech, 2011). This results in possible maltreatment of part of the group because patients with one and the same diagnosis might need different treatments depending on factors like severity or chronicity. Nevertheless, these varying outcomes in studies on treatment effects, depending on the composition of the groups (Paris, 2014), might mislead researchers and clinicians when those outcomes are generalized to the whole group. When focusing on patients with chronic psychiatric disorders, one often needs to give special attention to an accompanying group of disorders such as sleep disorders. Sleep structure disturbances in these patients are associated with, among other things, memory deficits; thus, an effective treatment of their sleep should improve not only sleep but also the associated memory impairments (Göder, Nissen, & Rasch, 2014).

Chronic Illness

Chronic (or long-term) psychiatric illness is described as a situation in which the patient has suffered from a disorder for at least five years without having had a symptom-free period that lasted longer than six months (Robins, 1978). One important aspect in these patients that needs consideration is demoralization (O'Keeffe & Ranjith, 2007). Demoralization can be described as a response that may follow chronification of the disease, which has been, for instance, found in patients with schizophrenia (Restifo, Harkavy-Friedman, & Shrout, 2009) and depression (Koekkoek, van Meijel, Schene, & Hutschemaekers, 2008). Depression and demoralization have been described as separate states since the 1970s. Demoralization may be described as a lost sense of one's own capability whereas patients suffering from depression are not capable of using their capacity (Jacobsen, Maytal, & Stern, 2007).

Sleep Disorders and Psychiatric Disorders

Ample evidence exists for an association between psychiatric disorders and various sleep disorders (Buysse et al., 1994; Sateia, 2009); moreover, previous research has shown that when sleep disorders are untreated, the risk of developing psychiatric disorders, such as major depression, increases (Ford & Kamerow, 1989). In their study, Hsu, Liu, and Chen (2006) found that 65.8% of patients referred to sleep-disorder centers were suffering from a psychiatric disorder. Depression (Urilla et al., 2012), anxiety (Staner, 2003), and substance

abuse (e.g., drugs, alcohol, etc.) (Conroy & Arnedt, 2014) are among the most common psychiatric disorders associated with sleep problems. Sleep disorder treatment was found to improve the co-existing psychiatric condition and the overall health-related quality of life of psychiatric patients (Matteson-Rusby, Pigeon, Gehrman, & Perlis, 2010). Before discussing sleep disorders and coexisting schizophrenia or depression, I will first describe the diagnostic criteria for sleep disorders.

Sleep Disorders

A sleep disorder, also called somnipathy, is a medical disorder in which the usual sleep pattern is disturbed. In a condition like this, an unsatisfactory quantity and/or quality of sleep is present over a significant period of time. Thereby, the person has difficulties falling and/or staying asleep, and the final wakening may be early. As can be seen in Table 3a, according to the ICD-10 (World Health Organization, 1992), sleep disorders are classified under F51.0-F51.9 nonorganic sleep disorders or under G47.0-G47.9 organic disorders. Non-organic sleep disorders are diagnosed when the sleep disorder is perceived as a condition in itself. Organic sleep disorders have an identifiable physical cause.

Table 3a.

According to the ICD-10 (World Health Organization, 1992), the following characteristics are used in the classification of non-organic sleep disorders.

Classification sleep disorder:

- A complaint of excessive daytime sleepiness or sleep attacks or prolonged transition to the fully aroused state upon awakening (sleep drunkenness) (not accounted for by an inadequate amount of sleep).
- Occurrence nearly every day for at least one month or recurrently for shorter periods of time, causing either marked distress or interference with personal functioning in daily living.
- Absence of auxiliary symptoms of narcolepsy (cataplexy, sleep paralysis, hypnagogic hallucinations) or of clinical evidence for sleep apnea (nocturnal breath cessation, typical intermittent snorting sounds, etc.).
- Absence of any known causative organic factor, such as a neurological or other medical condition, psychoactive substance use disorder or a medication.

Subtype classification:

- F51.0 Nonorganic insomnia
- F51.1 Nonorganic hypersomnia
- F51.2 Nonorganic disorder of the sleep-wake schedule
- F51.3 Sleepwalking [somnambulism]
- F51.4 Sleep terrors [night terrors]
- F51.5 Nightmares
- F51.8 Other nonorganic sleep disorders
- F51.9 Nonorganic sleep disorder, unspecified
- G47 Sleep disorders
- G47.0 Disorders of initiating and maintaining sleep (insomnias)
- G47.1 Disorders of excessive somnolence (hypersomnias)
- G47.2 Disorders of the sleep-wake schedule
- G47.3 Sleep apnoea
- G47.4 Narcolepsy and cataplexy
- G47.8 Other sleep disorders
- G47.9 Sleep disorder, unspecified

As can be seen in Table 3b, according to the DSM-5 (American Psychiatric Association, 2013), sleep-wake disorders encompass 10 disorders or disorder groups. The key features of each disorder is related to the patient's dissatisfaction with respect to the timing, quality, and total sleep quantity, thus leading to daytime distress and impairment.

Table 3b.

The 10 disorders or disorder groups that encompass the classification sleep-wake disorder according to the DSM-5 (American Psychiatric Association, 2013).

- Insomnia disorder
- Hypersomnolence disorder
- Narcolepsy
- Breathing-related sleep disorders
- Circadian rhythm sleep disorders
- Non-REM (NREM) sleep arousal disorders
- Nightmare disorder
- REM sleep behavior disorder
- Restless legs syndrome
- Substance- or medication-induced sleep disorder

The International Classification of Sleep Disorders Version 2 (ICSD-2) (American Academy of Sleep Medicine, 2005) can be used for diagnostic procedures. Accordingly, parasomnias can be divided into three categories, i.e., 'partial arousals during non-REM sleep,' 'REM-sleep parasomnias,' and 'other parasomnias.' The first category consists of sleep walking, confusional arousals and pavor nocturnus (sleep terror), usually occurring during sudden awakenings out of 'slow-wave sleep' (SWS) (Broughton, 2000). The second category mostly occurs during the shift from REM sleep to wakefulness and consists of 'REM-sleep behavior disorder' (RSBD), nightmares and sleep paralyses. The remaining category consists of parasomnias that do not specifically present themselves during a certain stage: nocturnal enuresis or bedwetting, sleep-related dissociative disorder, 'exploding head syndrome,' sleep-related eating disorder (SRED), catathrenia or nocturnal expiratory groaning, and hypnagogic hallucinations (Mason & Pack, 2007).

Sleep Disorders and Coexisting Schizophrenia

From daily clinical practice, patients with schizophrenia are known to suffer from problems with sleep (Wilson & Argyropoulos, 2012). Disturbed sleep can be found in 30-80% of patients with schizophrenia; this large difference in percentages can be explained by the severity of the psychotic symptomatology (Cohrs, 2008).

Studies that used polysomnography have found that patients with schizophrenia show decreased total sleep time, increased sleep latency, and decreased sleep efficiency (Chouinard, Poulin, Stip, & Godbout, 2004; Monti & Monti, 2004, 2005). In addition, alterations of slow-wave sleep (Göder et al., 2004) and REM sleep variables, such as reduced REM latency (Monti et al., 2013; Poulin, Daoust, Forest, Stip, & Godbout, 2003) and REM

density (Cohrs, 2008), have been found. Therefore, although sleep disorders are not among the first symptoms that come to mind when thinking of schizophrenia, they seem to be a part of its pathophysiology and should not be underestimated (Cohrs, 2008).

Sleep Disorders and Coexisting Depression

The majority of patients with depression suffer from sleep disorders (Nutt, Wilson, & Paterson, 2008), varying from problems with falling asleep to early morning awakening, difficulties in staying asleep, or non-refreshing sleep. Excessive daytime sleepiness is also reported in these patients (Fava, 2004); however, this is peculiar to a subtype of depression that is found in patients suffering from seasonal affective disorder (Øyane, Ursin, Pallesen, Holsten, & Bjørvatn, 2008).

Research in patients with depression has revealed prolonged sleep latency (time to fall asleep) and reduced rapid-eye-movement (REM) sleep latency (time to REM sleep from sleep onset) compared to healthy control participants (Dahl et al., 1996). In addition, a decrease in the amount of slow-wave sleep and an increased amount of REM sleep and REM density have been found in patients with depression (e.g., Palagini, Baglioni, Ciapparelli, Gemignani, & Riemann, 2013).

Failure to treat insomnia increases the risk of a depression relapse (Franzen & Buysse, 2008). Several cross-sectional studies (e.g., Breslau, Roth, Rosenthal, & Andreski, 1996; Eaton, Badawi, & Melton, 1995; Chang, Ford, Mead, Cooper-Patrick, & Klag, 1997; Livingston, Blizard, & Mann, 1993) revealed that symptoms of depression and insomnia are strongly associated; moreover in cases where insomnia is present, the chances of developing depressive episodes and showing poor treatment results are increased (Franzen & Buysse, 2008).

Pharmacological Treatment

Pharmacological interventions have been developed for the treatment of patients suffering from schizophrenia, depression and/or (coexisting) sleep disorders. Patients with schizophrenia have been treated with several antipsychotics, starting with the so-called first generation drugs such as chlorpromazine, followed by antipsychotics of the second generation. Nevertheless, the list of adverse effects of these medications is long, and compliance has always been, and still is, an issue for patients with schizophrenia (Haller, Padmanabhan, Lizano, Torous, & Keshavan, 2014). Several pharmacological treatments can be used for patients with depression, and discussions on their efficacies are ongoing (Paris, 2014). As to medications for sleep disorders with or without comorbid psychiatric disorders, 10 to 17% of the American population has recently been found to use sleep medications regularly (Vaidya, Hufstader-Gabriel, Gangan, & Borse, 2014). Because all of these treatments have their own side effects and none actually cures the disorder for which it is given, different treatment methods should be sought.

In addition to these pharmacological treatments for schizophrenia, depression, and sleep disorders, other cultures have different approaches that they have already implemented in allopathic medicine. In Asia, for instance, several branches of Traditional Oriental Medicine (TOM) have been integrated into psychiatric care. One part of TOM is acupuncture, a technique involving the insertion of needles that originated in China within the so-called Traditional Chinese Medicine (TCM). Acupuncture is now used alongside allopathic medicine as a non-pharmacological add-on treatment. Besides China, it is used in Korea (where it is called Traditional Korean Medicine or Hangul), Japan (where it is called Kampō), Tibet (where it is called Traditional Tibetan Medicine), etc. First, I will first briefly summarize part of the philosophical background of this ancient technique and its key critical methodological issues, before discussing the results that have been found in research on acupuncture treatment for schizophrenia, depression, and sleep disorders.

Acupuncture and Its Traditional Chinese Medicine Background

TCM contains a broad range of medical practices besides acupuncture: for instance herbal medicine, Feng Shui, dietary advice, Qi Gong (exercises) and Tuina (massage). In TCM, Qi (life's vital energy) is believed to be transported through "highways" or meridians that flow through the body. These meridians might get blocked (like a traffic jam on the highway), in which case the police (needles; for an example, see Figure 1) might be used to get the traffic going again at the end of the line or to stop more cars from arriving at the beginning of the road. This metaphor might explain why symptoms like, for instance, a headache might be treated by inserting needles into the head, but also by inserting needles into the feet or somewhere in between. TCM theory is philosophical and it is based on principles like Qi, Yin and Yang, the Zang-Fu organs, and the Five Elements (Cheng, 1987).

Figure 1. Examples of common acupuncture needles used in the current Ph.D. project (with permission of the CMC Tasly Centre, Amsterdam).

When these concepts of TCM are compared to Western medicine, some similarities can be found. About 2000 years ago, Hippocrates started personality studies with the four humors, (see page 45 in Wittendorff, 1994). This ancient medical concept of humorism suggests that four bodily fluids affect human personality traits and behaviors. This theory hypothesizes that our bodies are filled with four basic substances that are called "humors". These substances are thought to be in balance when a person is healthy. Excesses or deficits of one or more of these four humors inevitably result in diseases and disabilities. The fluids are described as phlegm and blood, and yellow and black bile. An excess of yellow bile results in a choleric person and makes that person quick-tempered. Too much black bile indicates a melancholic and pessimistic person. A phlegmatic person has an excess of phlegm, which results in a sluggish and calm temper. A high level of blood makes a person sanguine and is characterized by a cheerful, passionate tendency (see page 45 in Wittendorff, 1994). These four humors are closely related to the elements and/or seasons, that form the pillars of TCM (Han, 2008). They can be seen as a basis for an explanation of the mind-body connection from both a Western and an Eastern point of view. In TCM, the relation between body and mind is often described as the integration of essence (*Jing*), energy (*Qi*) and mind or spirit (*Shen*) (Yang, 2008). In this philosophical description, *Jing* can be seen as the biological basis of body and mind. It is formed by the so called pre-heaven essence that is inherited from one's parents (this might be seen as the ancient equivalent of DNA), and by the post-heaven essence, which is consumed from that which is taken in by our bodies: food, fluids, and breath. *Jing* forms the organs and the bodily structure, including the brain, the nervous system, and the endocrine system (Yang, 2008).

The classical assumption in TCM is that, in the process of development, *Jing* generates marrow which rises up to form the *Sea of marrow* (the brain). *Jing* is the material basis of all physiological functions of all organs. When *Jing* is weak or blocked, mental problems arise (Yang, 2008). In addition, *Qi* is translated as energy (Cheng, 1987). It is formed from the inherited life power (also called pre-heaven *Qi*), the essence that arises from the transformation of food, fluids, and the air we breathe. *Qi* is the force that fluently moves through the body and that promotes a normal functioning of the body (Cheng, 1987). *Qi* leaves the body at death. Pathological conditions can be described with help of the *Qi* concept: *Qi* can stagnate or move in the wrong direction and this might be the cause of physical or mental disorders. Moreover, as everything is connected, so are *Jing* and *Qi* (Yang, 2008). One more important aspect in explaining mental disorders, according to TCM theory, is *Shen*. Shen is the manifestation of *Qi* and *Jing* in relation to knowledge, emotions and behavior (Yang, 2008). Enough *Jing* and *Qi* flowing fluently are the basis for stabile mental activity. A disturbance of either can lead to mental emotional problems.

In TCM, different "patterns of disharmony" that somehow obstruct the free flow of *Qi* and thereby influence emotions, behavior and mental activity overall are described (Gao, 1982).

Disharmony may occur because of problems with or due to *Qi*, *Essence*, *Blood* (a vital nutrient substance in the body according to TCM; Cheng, 1987), *Body Fluids* (a collective term for all the normal fluids of the body; Cheng, 1987), the meridians, or the *Zang-Fu* organs. Some explanation is needed here when it comes to these latter concepts. Twelve main meridians, 8 extra meridians, 12 divergent meridians, 12 muscle regions, and 12 cutaneous regions exist (He & Tan, 1998). All of these are responsible for the circulation of *Qi* and *Blood*. The meridians and collaterals are distributed both interiorly and exteriorly across the body (Cheng, 1987). The *Zang* and *Fu* organs are functional entities situated interiorly and manifested exteriorly. Each organ is considered to be *Yin* (the *Zang* organs) or *Yang* (the *Fu* organs), and all organs are thought to belong to one of the five elements. The *Zang-Fu* organs are the center of the philosophical explanation of how the body works according to TCM (Zhang, Ming 1563-1640). All so-called "organs" have their own functions. When a disharmony occurs, the theory on the *Zang-Fu* organs can be used in order to find the origin of the disharmony and, accordingly, to create a treatment plan that uses acupuncture needles to influence the meridians and thereby the *Zang-Fu* organs in order to re-establish harmony. One more important concept that needs to be mentioned is the *Five Element Theory*. Everything in the natural world can be classified according to their nature, function and form into the *Five Elements* (*Wood, Fire, Earth, Metal, Water*). The *Five Elements* are in a state of constant motion and change; if harmony exists, they depend on each other and are inseparable (Cheng, 1987). In clinical practice, a pattern is sought that best describes the situation of the patient, with all his or her symptoms and signs. In order to decide where needles should be inserted, a TCM practitioner will conduct diagnostics before each treatment, investigating all of the above-mentioned ideas and will arrive at a diagnosis by using the five diagnostic methods that are used in TCM: inspection, auscultation, olfaction, inquiry, and palpation, including tongue and pulse diagnosis. After information has been gathered by using all these methods, a pattern of disharmony is diagnosed, and treatment is planned accordingly. In the TCM tradition, this pattern is called a diagnostic pattern.

Working Mechanisms Behind Acupuncture

Although TCM has a philosophical background and its working mechanisms have been explained by the above-mentioned theories, its physical mechanisms have not been measured and "proven" from a Western point of view. In fact, although many ideas on the working mechanisms behind acupuncture have been published, its exact effects on the body and mind are unknown. At the moment, research into the neurobiological mechanisms by using neuroimaging techniques is flourishing (Bai et al., 2014). However, although many hypotheses have been formed, no clear mechanism has arisen from the growing number of studies. In veterinary studies, a search for the involved neurotransmitters is ongoing (Fry, Neary, Sharrock, & Rychel, 2014). In response to needle irritation of a local area, certain neurotransmitter levels are influenced; among these are met-enkephalin and substance P along the nociceptive pathway, the luteinizing hormone via the hypothalamus pituitary axis,

and the level of serotonin and dopamine in the limbic system (Cheng, 2014). All in all, many questions remain unanswered regarding the mechanism behind acupuncture, and research is ongoing.

Acupuncture and Guidelines for Research

The Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) were first formulated in 2001 (MacPherson et al., 2010a, 2010b) and are aimed to improve the completeness and transparency of acupuncture research by providing sufficient details in order to facilitate replication and interpretation. In addition to the style of acupuncture (manual acupuncture, laser acupuncture, electro acupuncture, etc.), the reasoning for the treatment (meaning the choice of treatment, which might differ slightly between the schools of TCM that all use the same philosophical background, but differ when it comes to the choice and the order of treatment principles), the extent to which treatment varies, the details of needling (number of needle insertions, needling locations and depths, responses sought, needle stimulation, needle retention times, needle types), the treatment regimen (number of sessions, frequencies and durations of the treatment sessions), other components of treatment (details of other interventions, as well as the setting and the context of treatment), the practitioner's background, and controls or comparator interventions need to be addressed and discussed in research reporting on the effects of acupuncture (MacPherson et al., 2010a, 2010b).

Critical Methodological Issues in Acupuncture Research

Several important methodological issues in acupuncture need to be taken into account. Some of these are typical for acupuncture and some concern research in general. One issue is the presence of a control group. TCM studies on the clinical effect of acupuncture often have not used a control group, reasoning that *not* treating a patient would be unethical (Bosch, Ausfeld, & Van den Noort, 2008). As a result, older TCM studies investigating the clinical effect of acupuncture in a psychiatric population frequently consisted of one or more case studies (Shi & Tan, 1986; Shi, 1988, 1989).

In recent years, acupuncture researchers have tried to develop a successful control intervention. For the development of good acupuncture placebo interventions, both the physiological activity of the control intervention as well as the way in which the control intervention may activate the "placebo" response must be taken into account (Bosch et al., 2008). If, for instance, "non-acupuncture point needling" is used in the control group, physiological acupuncture effects are implied, resulting in effects that are often close to those found in the real acupuncture group (Streitberger & Kleinhenz, 1998). Following these results, three different conclusions are possible: (1) Acupuncture is not point specific, meaning that where the needles are inserted does not matter; an effect will always be observed. (2) Acupuncture is based on a placebo effect. (3) Acupuncture is point specific, but acupuncture needles in meridian zones result in an effect that is larger than no acupuncture,

but smaller than acupuncture at a "true" acupuncture point. In other acupuncture studies, very different treatments, such as transcutaneous electrical nerve stimulation (TENS) (Dias, Vellarde, Olej, Teófilo Salgado, & de Barros Rezende, 2014) or low-intensity high-frequency electro-stimulation treatment (Johansson et al., 2001) have been used in the control group; thus, whether or not the effects that are found when the effects of the control group are deducted from the effects of the treatment group are due to acupuncture is unclear. In the above-mentioned studies, a design was chosen that should compare a treatment to a placebo, thereby eliminating a possible psychological placebo effect and creating the opportunity to conclude something about the actual treatment effects. In the above-mentioned studies, however, whether the effects that were found in the control group were only the result of a psychological effect or were actually the result of the control group's treatment was not clear (Streitberger & Kleinhenz, 1998). Despite considerable intellectual and practical efforts on designing and testing placebo controls in acupuncture research (Vickers, 2002), researchers have not found and have not reached agreement with respect to a convincing and proven "placebo" for acupuncture (Moroz et al., 2013). Nevertheless, several controls such as the placebo-needle, sham acupuncture, and double-blind experiments, have been tried and found to be useful to a certain degree (White, Golianu, Zaslawski, & Seung-Hoon, 2007). I will discuss them in more detail below.

One attempt by the acupuncture researchers to find a suitable control was the development of an instrument that gave the participant the sensation of an acupuncture needle. That instrument is the so-called "placebo-needle", and in recent years, different kinds of placebo-needles have been developed (e.g., Park, White, Stevinson, Ernst, & James, 2002; Streitberger & Kleinhenz, 1998; Takakura & Yajima, 2008). However, placebo-needles have their limitations. First, they cannot be applied to all acupuncture point locations, for instance, the acupuncture points on the toes, fingers, and scalp (Kaptchuk, 1998). Secondly, the placebo-needle method does not allow significant variations in manual stimulation methods or diversity in needle-insertion directions (Kaptchuk, 1998), and nearly 40% of the participants did not find that the placebo-needle and the acupuncture interventions felt the same, raising concerns with respect to the use of the placebo-needle as a standard acupuncture placebo (White, Lewith, Hopwood, & Prescott, 2003). Thirdly, sham needles are expensive (in comparison with standard acupuncture needles). Finally, the largest limitation, however, is the fact that the placebo-needle method does not solve the problem of double blinding, meaning the masking of the practitioner (if a practitioner is to insert a needle, he or she feels the difference between a placebo needle and a real one) (Kaptchuk, 1998).

Another attempt is nowadays known as "sham acupuncture", in which needling is conducted on places on the body that are away from the classical acupuncture points, but the depth of insertion and the stimulation are the same as in real acupuncture (Vincent & Lewith, 1995; for examples, see Deng et al., 2013; Foroughipour et al., 2014). Moreover, in sham acupuncture, acupuncture points may be stimulated without inserting a needle or with

needles that are only superficially inserted. However, a serious limitation of sham acupuncture is that stimulation of a point without inserting a needle may also lead to a therapeutic effect (Lund & Lundeberg, 2006). Furthermore, Traditional Japanese Medicine works with superficial needling only; thereby, some sham treatments might have been nothing more than a different acupuncture technique instead of a control treatment.

One more methodological problem is whether acupuncture treatment should be standardized or individualized in clinical studies on the efficacy of acupuncture (Pach et al., 2013). In individualized treatment, one keeps as close as possible to daily clinical TCM practice that any (psychiatric) patient would receive if he or she were being treated by an Oriental medical practitioner (Bosch et al., 2013). From a pure scientific point of view, one would prefer as much standardization as possible; however, one must keep in mind that studies that test acupuncture within its own medical traditions seem to give a more appropriate and more clinically meaningful assessment of acupuncture's efficacy (Hammerschlag, 1998). The choice of a research design using individualized treatment or a standardized treatment protocol, in comparison with another control group (some sort of sham acupuncture or a different kind of control group), inevitably raises a basic question: What is the research question being asked? Are we asking the question whether acupuncture is better than a sham acupuncture which was found to be highly different from a placebo treatment (Vincent and Lewith, 1995)? Real (standardized or individualized) acupuncture, in comparison with sham acupuncture (in which sham points are used), would in that case only provide information on the role of the point's location. If acupuncture is not point specific, the results for all groups should be the same. The same goes for superficial needling versus deeper needling, or even just touching of the skin, in which case one would be comparing two or three kinds of treatment, instead of one treatment to a placebo, as was intended in the first place. Thus, questioning whether acupuncture should be compared to a placebo seems reasonable, or to describe it in line with MacPherson's (2000) words: the question should be whether acupuncture is of better value than what is currently on offer, instead of asking whether acupuncture is better than placebo.

Clinical acupuncture studies are designed to be either pragmatic or explanatory (MacPherson, 2004). A pragmatic clinical study is designed in a way that allows the effectiveness of a treatment (in this case acupuncture) in real clinical practice to be determined (Godwin et al., 2003). On the other hand, explanatory clinical studies are designed in order to determine whether acupuncture treatment has an efficacy, as compared to a placebo, under ideal experimental conditions (MacPherson, 2004). In pragmatic clinical studies, the researcher tries to find a balance between the external validity (in other words the generalizability of the results) of the study on the one hand and the internal validity (the reliability or accuracy of the results) of the study (Godwin et al., 2003) on the other. In contrast, the explanatory clinical study tries to maximize the internal validity of the study by having rigorous control of all variables other than the clinical (acupuncture)

intervention. Examples of these are the double-blind, randomized, placebo-controlled trials of acupuncture (Ng et al., 2004; Rebhorn et al., 2012). In pragmatic clinical acupuncture studies (MacPherson, Thorpe, & Thomas, 2006; Martins, Kaster, Schützler, & Witt, 2014), the researcher tries to maximize external validity, making generalizability of the results possible; however, the risk of pragmatic clinical acupuncture studies is that the internal validity may be severely compromised in order to ensure the generalizability (Godwin et al., 2003).

In sum, to date, acupuncture research has no such thing as a "golden" methodological study design, which presumably will remain a hot and highly-discussed topic in the years to come. All designs that have been developed and proposed by researchers within the acupuncture field have their own strengths and limitations, varying from high external validity to high internal validity. Depending on the research question and the aim of the study, the researcher needs to select the best design. In the present Ph.D. project, different kinds of study designs were used, depending on the research questions and aims of the study, as well as on the research possibilities in daily clinical practice with psychiatric patients.

Acupuncture in Depression

The overall results on the use of acupuncture to treat patients with depression seem promising. Acupuncture was found to be an effective, safe, and cost-effective therapy in treating major depressive disorders (e.g., Spackman et al., 2014; Qu et al., 2013; Wang et al., 2008; Wang, Wang, Tao, & Chen, 2014; Zhang et al., 2010). Yeung, Ameral, Chuzi, Fava, and Mischoulon (2011), for instance, conducted a study on 30 patients with depression in order to investigate the efficacy of acupuncture in treating patients who had responded partially or not at all to antidepressants. They found that the use of acupuncture once or twice a week was safe and that patients tolerated it well. More importantly, they found acupuncture to be an effective treatment intervention in patients with depression, who were responding either partially or not at all to antidepressants therapy. Yeung et al. (2011) concluded that their results suggested the feasibility of using acupuncture for the treatment of patients with depression in outpatient settings, but that replication in controlled trials was needed before firm conclusions could be drawn. Acupuncture was found to be a safe and well-tolerated monotherapy (Mischoulon, Brill, Ameral, Fava, & Yeung, 2012), as well as a safe and well-tolerated add-on treatment in addition to antidepressants (Wu, Yeung, Schnyer, Wang, & Mischoulon, 2012). Even though patients with depression have shown improvements in depressive symptoms after acupuncture treatment (Andreescu, Glick, Emeremni, Houck, & Mulsant, 2011), caution is required regarding these positive clinical treatment effects (Smith, Hay, & MacPherson, 2010) because, for instance, Ernst, Lee, and Choi (2011) and Leo and Ligot (2007) drew the conclusion that the effectiveness of acupuncture as a treatment for patients with depression remained unproven and was too premature and that more, larger, methodologically-better-designed Western studies on acupuncture and depression were needed (Ernst, Lee, & Choi, 2011; Wu et al., 2012).

Acupuncture in Schizophrenia

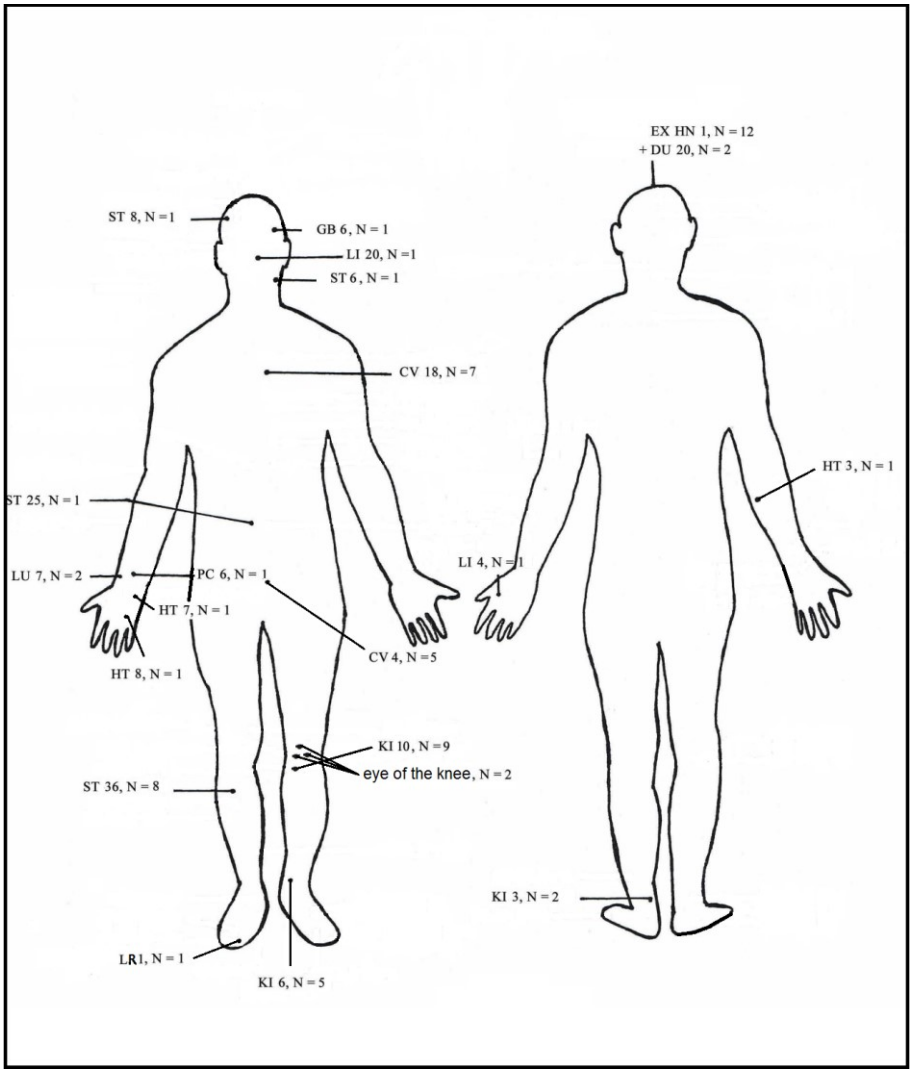

Figure 2. Example of the acupuncture treatment of a patient suffering from schizophrenia (Bosch, Staudte, & Van den Noort, 2014).

The number of acupuncture studies on schizophrenia is much smaller than the number of acupuncture studies on depression (for an example of the acupuncture treatment of a patient suffering from schizophrenia, see Figure 2). So far, only a few clinical studies have been conducted on acupuncture and schizophrenia, most of which originated from China (Lee, Shin, Ronan, & Ernst, 2009). In the study by Bloch and colleagues (2010), sleep was found to be improved after acupuncture treatment; moreover, the patients with schizophrenia showed less anxiety and an improved mood after acupuncture therapy. The overall results of the clinical trials and the case studies on patients with schizophrenia provided limited evidence for the effectiveness of acupuncture in treating the 'symptoms' of schizophrenia (e.g., Bouhlel et al., 2011; Lee et al., 2009; Rathbone & Xia, 2005). Nevertheless, in some research, positive results in the treatment of hallucinations by using acupuncture were reported (Shi, 1988, 1989). In several studies, the hallucinations entirely

disappeared (Wu & Bi, 2004; Zhang, 1988) or their number decreased (Wu & Bi, 2004; Zhang, 1988); furthermore, in a single case study, the severity of the hallucinations decreased (Bosch, Staudte, van den Noort, & Lim, 2014), and the patient felt less disturbed. In other studies, not only sleep quality but also the quality of life seemed to be improved in patients with schizophrenia as a result of acupuncture treatment (e.g., Bosch et al., 2013; Bosch et al., 2014; Reshef et al., 2013). Tani, Suzuki, Takada, Yagyu, and Kinoshita (2005), for instance, found a positive effect of acupuncture therapy in treating the side-effects of long-time drug use in a patient with chronic schizophrenia. Acupuncture treatment was reported to have a positive effect on tardive dystonia, including axial dystonia; the posture of the neck and body improved, and the involuntary movement disappeared completely. Moreover, Xu, Su, and Wang (2010) found that the combined therapy of acupuncture and a small dose of antipsychotics showed an efficacy equal to that of a full dose of antipsychotics and that the combined therapy had several important advantages: a shorter initiation time and fewer side effects compared to treatment with a full dose of antipsychotics. However, the results of systematic reviews, as well as comparative and case studies, need to be interpreted with caution because more, larger and methodologically-sound studies on acupuncture and schizophrenia are needed (Lee et al., 2009; Rathbone & Xia, 2005) before any firm conclusions on the possible effects of acupuncture treatment on the symptoms of patients with schizophrenia can be drawn.

Acupuncture in Sleep Disorders

The overall results of clinical studies, most of which were randomized, controlled, clinical trials, on the use of acupuncture to treat insomnia have shown positive effects (Cao, Pan, Li, & Liu, 2009; Zhao, 2013). Several studies showed acupuncture treatment to be effective in the treatment of insomnia (e.g., Da Silva, Nakamura, Cordeiro, & Kulay, 2005; Guo et al., 2013; Kim et al., 2004). Moreover, acupuncture can be as, or even more, effective than conventional pharmacological treatment with drugs, such as trazodone, zolpidem, or estazolam, in the treatment of insomnia (Luo, Zhang, & Lai, 2010; Tu, Chung, Yang, & Tzeng, 2012; Xuan, Guo, Wang, & Wu, 2007). Although acupuncture was found to be a safe clinical intervention (Huang, Kutner, & Bliwise, 2009) and showed great potential to be an effective treatment for insomnia (Huang et al., 2009), its positive results are less than certain because of methodological limitations (Zhao, 2013) such as a high risk of bias (Cheuk, Yeung, Chung, & Wong, 2012). In addition, the majority of clinical acupuncture studies on insomnia are heterogeneous in the way insomnia, the participants' characteristics, the acupuncture points, and the treatment regimen have been defined (Cheuk et al., 2012). Therefore, high-quality clinical studies with randomized, controlled trials on larger samples (Cao et al., 2009) and with longer follow-up measurements in order to measure the sustained effects of acupuncture (Carlsson, 2002) are required in future research on the its efficacy for the treatment of patients with insomnia (Cheuk, Yeung, Chung, & Wong, 2007).

Outline

Aim of the thesis

This thesis investigates a possible add-on treatment for patients with schizophrenia and depression. Acupuncture effects on sleep and psychopathology are studied. The research questions areas follows: (1) What possible problems in sleep, psychopathology and working memory performance can be found in a population of long-term patients with schizophrenia and patients with depression? (2) Does acupuncture improve the patients' sleep? (3) Does acupuncture decrease the patients' psychopathology? (4) Does acupuncture improve the patients' working memory performance?

First, in Chapter 2, a study is presented that characterizes our patient population. More specifically, whether the long-term illness (chronicity) of the patients with depression or schizophrenia itself might influence the score on a personality inventory; the Minnesota Multiphasic Personality Inventory-2, was investigated. Whether chronicity itself might have a differential effect on the profiles of these patients and whether demoralization 'associated with long-term illness' might affect the scales of the personality inventory was also studied. Thirty patients with long-term schizophrenia, 30 long-term patients with depression, and 30 healthy participants completed the personality inventory. Groups were compared on Clinical Scales and on the Restructured Clinical (RC) Scales.

Chapter 3 is an inventory of the parasomnias and other nocturnal behaviors in our population with depression and schizophrenia. These behaviors were determined by using a parasomnia screening test. In this chapter, 21 parasomnias and other nocturnal behaviors were assessed.

Chapter 4 describes a pilot study, in which the effects of three months of acupuncture treatment on sleep were evaluated and compared between a group of 16 patients with schizophrenia and a group of 16 patients with depression. In addition, eight healthy controls were included in order to establish reference values. Patients with schizophrenia and depression were randomly placed on a waiting list or assigned a treatment. A sleep quality inventory was completed by the patients who received acupuncture both before and after the treatment (individualized and according to Traditional Chinese Medicine principles) and by the patients who had been placed on the waiting list both at the beginning and at the end of the three month period.

Chapter 5 describes a preliminary clinical trial, in which the existence or not of a positive influence of acupuncture on sleep in patients with schizophrenia or depression was investigated. In total, 100 participants entered the study: 40 outpatients with schizophrenia, 40 outpatients with depression, and 20 healthy controls. They all completed a depression inventory, and the positive and the negative symptoms of the patients with schizophrenia

were evaluated by their psychiatrists. All participants were asked to complete a sleep log for two weeks. For the psychiatric patients, a randomized design with experimental (three months of acupuncture treatment) and control (waiting list) conditions was used, after which all measurements were conducted once more.

In Chapter 6, the question of whether acupuncture may be able to improve mood and working memory in patients suffering from depression or schizophrenia is addressed. In total, 50 patients with depression and 50 patients with schizophrenia were randomly divided into an experimental group and a waiting-list group. In addition, 25 healthy control participants entered the study. The patients in the experimental groups received twelve weeks of individualized acupuncture treatment, and a pragmatic clinical trial design was used. All patients in the experimental group were tested twice on a mood scale, a simple working memory task, and a complex working memory task both before (T1) and after (T2) acupuncture treatment; the waiting-list group was also tested twice, but without treatment other than their normal regimen. The healthy control participants were only tested at T1.

Chapter 7 contains a single case study. It describes the effect of acupuncture on the number and kind of hallucinations suffered by a patient with long-term schizophrenia. In addition, sleep quality, depressive feelings, and positive and negative symptoms were assessed. In one case, a 63-year-old woman suffered from persistent hallucinations and even physical pain as a result of the hallucination of a black bird that kept pecking her back. The patient received 12 weekly acupuncture treatments as an add-on treatment. A clinical diagnostic interview and psychological testing (on sleep quality, depression, and positive and negative symptoms) were conducted before, immediately after and three months after the acupuncture treatment.

In Chapter 8, the different TOM diagnostic patterns in patients with a Western diagnosis of schizophrenia, depression, or sleep disorders are described from a literature and a clinical perspective. Psychiatric disorders can be described and treated from both a Western (allopathic) and an Eastern perspective, which is important when research on acupuncture in psychiatry is conducted. Patients with schizophrenia or depression are likely to be undergoing Western treatment when they are referred to an acupuncturist for (add-on) treatment, and knowledge of both types of treatments is necessary to integrate them successfully. In this chapter, the diagnostic patterns that are found within our groups of 30 patients with depression and 30 patients with schizophrenia are presented and illustrate the problem encountered in research when comparing results from different studies containing different numbers of patients with different diagnostic patterns within the samples

In Chapter 9, the clinical evidence for the use of acupuncture as an add-on treatment for patients with depression and schizophrenia and the evidence on its working mechanisms are assessed. Four databases (Medline, Scopus, ERIC, and the Cochrane Library) were searched

until March 31, 2014. Systematic reviews of and meta-analyses on acupuncture treatment for patients with depression or schizophrenia were considered for inclusion. As a result of the scarce acupuncture research on schizophrenia, randomized controlled trials (RCTs) and case studies on acupuncture and schizophrenia were also included.

The main findings and implications of this research are summarized and discussed in Chapter 10.

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Chapter 2

The MMPI-2 in Chronic Psychiatric Illness

Based on:

Bosch, P., Van Luijtelaar, G., Van den Noort, M., Schenkwald, J., Kueppenbender, N., Lim, S., Egger, J., & Coenen, A. (2014). The MMPI-2 in chronic psychiatric illness. *Scandinavian Journal of Psychology, 55*(5), 513–519. doi:10.1111/sjop.12152

Abstract

While previous studies on the MMPI-2 in patients with schizophrenia and depression have used mixed samples of both early stage and chronic psychiatric patients, here, it is investigated whether chronicity itself might have a differential effect on the MMPI-2 profiles of these patients and whether demoralization 'associated with long-term illness' affects the scales of the MMPI-2. Thirty long-term patients with schizophrenia, 30 long-term patients with depression, and 30 healthy participants completed the MMPI-2. Groups were compared on Clinical Scales and on the Restructured Clinical (RC) Scales. Patients with schizophrenia differed from patients with depression on 14 MMPI-2 scales and from healthy controls on 10 scales, generally showing mean *UT*-scores < 65, indicating a subjective experience of (near) normal functioning. Patients with depression differed from healthy controls on 17 scales mostly with *UT*-scores > 65, indicating impaired functioning. Demoralization was higher in patients with depression than in patients with schizophrenia and both psychiatric groups differed from the healthy control group. It is concluded that long-term patients with depression show impaired functioning and high demoralization, while long-term patients with schizophrenia surprisingly show near normal functioning and less demoralization.

Introduction

The severity of psychopathology may differ over the years in patients with long-term (defined as a duration of at least five years after being diagnosed) schizophrenia (Bromet, Naz, Fochtmann, Carlson, & Tanenberg-Karant, 2005) and in patients with depression (Kennedy, Abbott, & Paykel, 2004).

An instrument that explores the self report of psychopathology and personality is the Minnesota Multiphasic Personality Inventory-2 (MMPI-2; Butcher et al., 2001), which comprises 567 self-report items. Most studies with the MMPI-2 on patients with schizophrenia as well as on patients with depression found significant differences from healthy controls on scales in the anxious-neurotic domain (e.g., 2-D, 7-Pt, 0-Si) and on scales that measure dysfunctions of interpersonal affect and emotion regulation (e.g., 4-Pd and 9-Ma scales; Ben-Porath, Butcher, & Graham, 1991; Munley, Busby, & Jaynes, 1997). In general, these studies have been performed in patients with various lengths of illness (both first-episode and chronic patients), which might have had an influence on the results (Nuechterlein & Dawson, 1984).

The first aim of this study was to investigate whether there are differences in MMPI-2 scales and profiles between patients with long-term schizophrenia and patients with long-term depression in comparison with each other and each with healthy controls. High levels of overall distress are expected for patients with depression due to their acute depressive symptoms (Wiersma et al., 2011), even in a long-term and chronic stage (see page 44, Wiersma et al., 2011), resulting in high scores (uniform *T (UT)*-score > 65) on their MMPI-2 profiles. On the other hand, clinically stable outpatients with schizophrenia report “normal” emotional responses to emotional stimuli (Hempel et al., 2005; Herbener, Song, Khine, & Sweeney, 2008; Schlenker, Cohen, & Hopmann, 1995), perhaps due to the character of the illness. Note that deficits in emotional functioning associated with schizophrenia seem to occur further downstream, and involve the successful integration of emotion and cognition required for adaptive functioning (e.g., goal-setting, motivation, memory, etc.) (Herbener et al., 2008).

Based on the literature findings, it is proposed that patients with schizophrenia will show lower scores than patients with depression on the 2-D, 7-Pt, 0-Si, 4-Pd, and 9-Ma (Ben-Porath et al., 1991; Munley et al., 1997) scales, although nevertheless higher than healthy controls, due to their long-term illness.

When it comes to explaining scores on questionnaires and tests performed by chronic patients, the concept of demoralization plays an important role (O’Keeffe & Ranjith, 2007). Demoralization may be seen as a somewhat normal response to a long and debilitating disease and has been found in patients with long-term schizophrenia (Restifo, Harkavy-Friedman, & Shrout, 2009) as well as in patients with long-term depression (Koekkoek, Van Meijel, Schene, & Hutschemaekers, 2008). Demoralization has been discussed as a state distinct from depression since the 1970s. Patients with depression cannot take a direction, whereas patients suffering from demoralization do not know what direction to take and experience a lost sense of efficacy (Jacobsen, Maytal, & Stern, 2007). Because patients with

long-term schizophrenia generally suffer more from stigmatization and less favorable long-term outcome expectancies than patients with long-term depression (Angermeyer & Matschinger, 2003), one might expect a larger demoralization effect in patients with long-term schizophrenia than in patients with depression. On the other hand, patients with depression often suffer from feelings of hopelessness and a persistent inability to cope, which might result in a larger demoralization effect. In sum, the question arises whether MMPI-2 profiles may be influenced by demoralization after a long period of a mental illness, and in which illness demoralization plays a larger role.

The MMPI-2 Restructured Clinical (RC) Scales were developed by Tellegen and colleagues (2003), partly to address MMPI-2 interpretation issues that may be related to demoralization (Van der Heijden, Egger, & Derksen, 2008). Another reason for developing the RC Scales was to eliminate the item overlap found among the MMPI-2 Clinical Scales (Tellegen et al., 2003). The RC Scales are not intended to replace the Clinical Scales. Differences between the Clinical Scales and the RC Scales are a result of removing the non-specific variance associated with demoralization, the K correction, and subtle items (Tellegen et al., 2003). With respect to demoralization, distinct from O'Keeffe & Ranjith (2007) who defined the concept as transient or understandable reactions to severe or life-threatening illness, Tellegen and colleagues (2003) used the Watson and Tellegen (1985) two-dimensional model of affect to explain the construct of demoralization. This mood model consists of two orthogonal bipolar dimensions, “Positive Affect or Arousal” and “Negative Affect or Arousal”, and a third dimension called “Pleasantness versus Unpleasantness”, positioned midway between the previously described two dimensions (Tellegen, Watson, & Clark, 1999a, 1999b). Unpleasantness is one pole of the dimension of general hedonic valence and according to Tellegen et al. (2003) this pole taps the essence of demoralization. After empirical study, the RCd scale was developed considering that demoralization lies in the middle between high negative emotion (anxiety) and low positive emotion (depression) (Ben-Porath & Tellegen, 2008).

Therefore, the second aim of our study is to investigate whether demoralization affects the MMPI-2 profiles in both patient groups. It is expected that both patient groups are demoralized (Koekkoek et al., 2008; Restifo et al., 2009) and this should lead to higher scores on the RCd scale, a scale that was specifically developed to embody the demoralization construct (Tellegen et al., 2003, p. 12). Moreover, since the other RC Scales were developed to exclude demoralization, it is hypothesized that patients will have lower scores on the RC Scales than on the Clinical Scales of the MMPI-2.

Methods

Participants

All participants entered the study on a voluntary basis and were not paid. The healthy controls were recruited by advertisements, whereas all patients were outpatients recruited at a psychiatric hospital in Germany. Diagnoses were based on clinical examination by

experienced psychiatrists of the clinic, using the International Classification of Diseases-10 (World Health Organisation, 1992). The Mehrfach-Wortschatz-Intelligenz-Test-B (MWT-B; Lehrl, 2005) was used as an inclusion criterion since an IQ of at least 80 is needed to complete the MMPI-2 correctly (Derksen, de Mey, Sloore, & Hellenbosch, 2006). Beck's Depression Inventory-II (BDI-II; Beck et al., 1996) was used as an inclusion criterion for patients with depression; at a cut-off score of 19, indicating (at least) a moderate depression (Beck, Steer, & Brown, 1996). The Positive And Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987) was used as an inclusion criterion for the schizophrenia group, at a cut-off score of 58 (e.g., Leucht et al., 2005). MMPI-2 profiles met the following inclusion criteria: Cannot Say < 30, VRIN and TRIN ≤ 80, Fp < 100, and L ≤ 80 (Butcher et al., 2001). A duration of illness of at least five years was used as a final inclusion criterion. Application of the MMPI-2 profile inclusion criteria resulted in the deletion of four participants (three out of the group with schizophrenia and one out of the control group). The exclusion criteria were: epilepsy, addiction or other neurological dysfunctions.

In total, 86 participants fulfilled all inclusion criteria. There were 27 males and 59 females and all participants were between 19 and 70 (M = 41.79, SD = 12.33) years old (see Table 1 for an overview of the average length of illness, number and length of hospitalizations, the MWT-B score, and the level of education specified for the schizophrenia, depression, and healthy control group). Seven participants, aged 19-64 (M = 41.70, SD = 10.83) of which 12 were males and 15 females, carried the diagnosis schizophrenia. Thirty participants aged 23-70 (M = 48.87, SD = 9.33) years of which six were males and 24 females, carried the diagnosis depression. The patients with schizophrenia had a significantly higher length of illness (p = .002, partial η^2 = .160), number of hospitalizations (p = .000, partial η^2 = .269) and length of hospitalization in days (p = .000, partial η^2 = .223) compared to the patients with depression, but the average intelligence (p = .560, partial η^2 = .006) and level of education (p = .976, partial η^2 = .000) did not differ between the two psychiatric groups. Finally, the control group consisted of 29 healthy participants aged 22-56 (M = 34.55, SD = 12.45) years of which nine were males and 20 females.

Table 1.

Descriptives of the schizophrenia, depression, and healthy control group.

	Schizophrenia		Depression		Healthy Controls	
Scale	*M*	*SD*	*M*	*SD*	*M*	*SD*
Length of illness[1]	17.91[a]	9.59	10.29	8.15	0	0
Average number of hospitalizations	4.52[a]	3.18	1.53	1.74	0	0
Length of hospitalization[2]	310.00[a]	287.39	87.40	103.58	0	0
MWT-B	102.89	16.18	99.93	10.88	104.19	9.53
Level of education[3]	3.07[b]	1.00	3.10[b]	.85	3.86	.35

Notes. [1] Length of illness in number of years, [2] Average length of hospitalizations in number of days, [3] The following scores were used according to the German education system (from low to high education): 1 = no education finished, 2 = Hauptschule, 3 = Realschule, and 4 = Gymnasium. [a] Mean score is significantly different

($p < .05$) from the mean score of the patient group with depression; [b] Mean score is significantly different ($p < .05$) from the mean score of the healthy control group.

Although there was a significant age difference between the groups, age was not found (analyses of covariance) to have a significant influence on the results on the Clinical (p = .509, partial η^2 = .138) or RC Scales (p = .472, partial η^2 = .105). The depression group contained three times more women; therefore, gender was used as covariate as well. No significant influence was found for gender on the Clinical Scales (p = .223, partial η^2 = .183) nor the RC Scales (p = .050, partial η^2 = .196). Moreover, no significant difference in intelligence (p = .618, partial η^2 = .013) was found between the three groups and the analyses of covariance showed that intelligence did not have a significant influence on the results on the Clinical (p = .724, partial η^2 = .121) or RC Scales (p = .503, partial η^2 = .113). Finally, a significant difference in level of education was found between the three groups (p = .000, partial η^2 = .197). As can be seen in Table 1, the healthy control participants on average had a significantly higher level of education as compared to the schizophrenia (p = .001) and depression groups (p = .000). The level of education was therefore examined as covariate as well. No significant influence was found for level of education on the Clinical (p = .381, partial η^2 = .156) or RC Scales (p = .780, partial η^2 = .070).

Clinical measures

MMPI-2

The MMPI-2 (Butcher & Rouse, 1996) is a psychopathology and personality inventory. Its psychometric qualities showed test-retest coefficients ranging from *rtt* =.62 to *rtt* = .92 (M = .83) for the Clinical Scales. Internal consistency coefficients range between α = .60 and α = .88 for the Clinical Scales (Engel, 2000).

The MMPI-2 has been used to distinguish patients with a depression from patients with schizophrenia (Ben-Porath et al., 1991), this despite some psychometric drawbacks, like a high inter-correlation among the Clinical Scales attributed to the First Factor (Rouse, Greene, Butcher, Nichols, & Williams, 2008). This prompted the construction of the RC Scales (Tellegen et al., 2003). It was subsequently established that the RC Scales show satisfying reliability and internal validity (Van der Heijden et al., 2008).

Specific Clinical Scales of the MMPI-2 have been found to show differences between schizophrenia and depression: 2-D, 9-Ma, 7-Pt (Ben-Porath et al., 1991; Munley et al., 1997), 4-Pd, 0-Si (Munley et al., 1997).

The RC Scale corresponding to Clinical Scale 2-D is RC2 (*Low Positive Emotions*); endorsement of the RC2 items indicates a lack of positive engagement in life. The RC version of scale 9-Ma is RC9 (*Hypomanic Activation*) which describes emotions, cognitions, attitudes and behaviors that are consistent with hypomanic activity. The RC version of the 7-Pt scale is RC7 (*Dysfunctional Negative Emotions*); elevated scores on this scale indicate a large number of negative emotional experiences; these patients tend to experience a high level of anxiety. The restructured version for 4-Pd is RC4 (*Antisocial Behavior*); it measures the tendency toward antisocial behavior. There is no RC equivalent for 0-Si.

MWT-B

The MWT-B (Lehrl, 2005) is a verbal intelligence test and consists of 37 lines with each five words. Four of them are non-words, and one is a true word that has to be found by the patient. Previous research found that the MWT-B correlates significantly r = .81 with the total IQ score from the HAWIE (Wiessner & Felber, 1981), indicating its reliability as an inclusion criterion in order to ensure sufficient capabilities to fill out the MMPI-2.

Procedure

Participants voluntarily entered the study, after receiving general information and signing for informed consent. Participants individually completed the MWT-B, BDI-II, and MMPI-2 during approximately two hours in a quiet room with a member of staff available for questions. The instruments were administered in accordance with the procedures described in the manuals. After the study, all participants were debriefed. The present study was approved by the local ethics committee (Ärztekammer Nordrhein) and followed the Declaration of Helsinki (World Medical Organization, 2008).

Statistical analyses

First, raw-scores for the Clinical Scales were used in a one-way multivariate analysis of variance (MANOVA) using SPSS version 19 (IBM Corp., 2010) to indicate whether the three groups differ significantly across the Clinical Scales. The dependent variables were the Clinical Scale-scores and the between-subjects factor was group (depression, schizophrenia, or healthy control). After a significant result on the one-way MANOVA, univariate ANOVAs were then conducted for each scale separately to determine which scales contribute to the multivariate difference between the groups. If appropriate, this was followed by post-hoc tests. A Sidak adjustment of the alpha level (.05) was used to correct for multiple tests. These analyses were repeated for the RC Scales.

Results

Clinical Scales

Mean *UT*-scores and *SD*s for the groups of patients with depression, schizophrenia, and the healthy controls were computed on the Clinical Scales. Patients with depression tended to have *UT*-scores > 65 on nine of the Clinical Scales, patients with schizophrenia reached this score on only Clinical Scale 2-D.

Table 2.

Mean UT-Scores, SDs, number of patients (and in percentages) that scored above 65, F, and η^2 on Clinical Scales of the schizophrenia, depression, and healthy control group.

	Schizophrenia			Depression			Healthy Controls				
Scale	*M*	*SD*	*>65*	*M*	*SD*	*>65*	*M*	*SD*	*>65*	*F* (2,83)	η^2
L	51.04[b]	9.79	4 (15%)	46.73	10.40	0 (0%)	40.90	8.05	0 (0%)	7.94	.16
F	62.33[a,b]	14.82	10 (37%)	73.87[b]	16.20	22 (73%)	50.69	10.48	2 (7%)	19.81	.32
K	48.04[a]	10.48	1 (4%)	38.10[b]	10.71	1 (3%)	50.03	9.89	1 (3%)	11.39	.22
1-Hs	55.07[a]	10.93	4 (15%)	69.77[b]	11.50	20 (67%)	48.86	8.88	1 (3%)	34.81	.46
2-D	65.48[a,b]	13.24	14 (52%)	79.67[b]	9.80	28 (93%)	50.17	11.27	4 (14%)	49.12	.54
3-Hy	60.89[a,b]	17.96	9 (33%)	69.03[b]	9.55	21 (70%)	47.97	8.39	1 (3%)	23.94	.37
4-Pd	64.85[a,b]	12.68	15 (56%)	74.33[b]	11.06	24 (80%)	53.59	11.52	3 (10%)	23.69	.36
5-Mf	52.04	11.31	3 (11%)	50.07	10.63	2 (7%)	45.97	13.73	0 (0%)	1.95/1.63	.05/.04
6-Pa	64.78[b]	14.86	13 (48%)	69.13[b]	12.87	15 (50%)	54.86	12.81	4 (14%)	8.70	.17
7-Pt	62.67[a,b]	12.68	12 (44%)	79.07[b]	11.05	27 (90%)	50.72	10.56	2 (7%)	47.06	.53
8-Sc	63.37[a,b]	11.39	14 (52%)	73.23[b]	10.82	22 (73%)	50.17	9.89	1 (3%)	33.79	.45
9-Ma	48.93	8.38	2 (7%)	53.60	8.88	3 (10%)	50.21	9.42	1 (3%)	1.61	.04
0-Si	55.96[a]	15.98	8 (30%)	71.03[b]	11.89	23 (77%)	48.79	11.52	3 (10%)	23.12	.36

Notes. MF consists of the *UT*-score of the MF scale, in the *F* and η^2 this consists of raw data MFM/MFV; [a]Mean *UT*-score is significantly different ($p < .05$) from the mean *UT*-score of the patient group with depression; [b]Mean *UT*-score is significantly different ($p < .05$) from the mean *UT*-score of the healthy control group.

The multivariate ANOVA showed significant group differences ($F_{(2,83)}$ = 5.845, p = .00, η^2 = .69). ANOVAs were therefore conducted separately for each of the Clinical Scales to indicate which of these significantly differentiated between the groups. As can be seen in Table 2, the depression group generally scored higher than the schizophrenia group; the control group generally scored lowest. Scores for the depressed group exceeded those of the schizophrenia group on the F, 1-Hs, 2-D, 3-Hy, 4-Pd, 7-Pt, 8-Sc, 0-Si scales, and scored lower on K (defensiveness). Moreover, the schizophrenia patients scored higher than the healthy controls on scales L, F, 2-D, 3-Hy, 4-Pd, 6-Pa, 7-Pt, and 8-Sc, while the depression patients scored higher on F, 1-Hs, 2-D, 3-Hy, 4-Pd, 6-Pa, 7-Pt, 8-Sc, 0-Si, and lower on the K-scale than the healthy controls.

RC Scales

While the depression group obtained *UT*-scores > 65 on four of the RC Scales, scores for the schizophrenia group failed to reach this level on any of these scales.

The MANOVA found significant group differences ($F_{(2,86)}$ = 7.358, p = .000, $\eta 2$ = .469), see also Table 3. ANOVAs and Posthoc analysis, the outcomes are presented in Table 3 as well, showed that the following scales were responsible for this result: The depression group scored higher than the schizophrenia group on RCd, RC1, RC2, RC3, and RC7. Additionally, the schizophrenia group scored higher than the controls on RCd, RC2, and RC8, while the depression group exceeded the controls on RCd, RC1, RC2, RC3, RC6, RC7, and RC8. The control group scored lowest on all scales that showed a significant group effect.

Table 3.

Mean UT-Scores, SDs, number of patients (and in percentages) that scored above 65, F, and η^2 on RC Scales of the schizophrenia, depression, and healthy control group.

	Schizophrenia			Depression			Healthy Controls				
Scale	*M*	*SD*	*>65*	*M*	*SD*	*>65*	*M*	*SD*	*>65*	*F* (2,83)	η^2
RCd	60.85[a,b]	12.06	9 (33%)	75.90[b]	8.21	27 (90%)	52.24	9.92	3 (10%)	46.38	.53
RC1	52.96[a]	11.34	5 (19%)	67.97[b]	13.57	15 (50%)	46.72	8.66	1 (3%)	30.38	.42
RC2	59.74[a,b]	13.54	8 (30%)	74.10[b]	12.07	21 (70%)	50.55	12.21	6 (21%)	26.80	.39
RC3	49.48[a]	14.01	3 (11%)	63.70[b]	12.96	16 (53%)	52.03	12.48	6 (21%)	8.04	.16
RC4	57.07	12.46	8 (30%)	61.53	10.31	12 (40%)	54.69	8.86	3 (10%)	2.76	.06
RC6	48.93	16.97	3 (11%)	54.43[b]	20.52	8 (27%)	40.79	16.05	2 (7%)	4.70	.10
RC7	55.44[a]	14.26	5 (19%)	68.47[b]	12.91	18 (60%)	51.38	9.51	3 (10%)	17.49	.30
RC8	57.89[b]	11.27	5 (19%)	60.60[b]	9.08	8 (27%)	46.69	8.18	0 (0%)	13.93	.25
RC9	45.33	9.10	1 (4%)	48.77	9.92	3 (10%)	52.03	10.28	5 (17%)	2.52	.06

Notes. MF consists of the *UT*-score of the MF scale, in the *F* and η^2 this consists of raw data MFM/MFV; RC = Restructured Clinical; RCd = Demoralization; RC1 = Somatic Complaints; RC2 = Low Positive Emotions; RC3 = Cynicism; RC4 = Antisocial Behavior; RC6 = Ideas of Persecution; RC7 = Dysfunctional Negative Emotions; RC8 = Aberrant Experiences; RC9 = Hypomanic Activation; [a]Mean *UT*-score is significantly different ($p < .05$) from the mean *UT*-score of the patient group with depression; [b]Mean *UT*-score is significantly different ($p < .05$) from the mean *UT*-score of the healthy control group.

Additional scales

Although our focus has been on the comparison of the Clinical and RC Scales among the depression, schizophrenia, and healthy control groups, for the sake of completeness MMPI-2 scores for the Harris-Lingoes subscales, the Content and Content Component scales, the Personality Psychopathology-Five (PSY-5), Superlative Self-Presentation subscales, and the Supplementary scales can be found in Table 4 (see supplementary material).

Discussion

The present study examined the MMPI-2 differences between long-term outpatients with schizophrenia or depression and healthy controls. The main outcomes were that unexpectedly, it was much harder to differentiate long-term patients with schizophrenia from healthy controls than to distinguish long-term patients with depression from healthy controls. This was especially the case from a single-case perspective because *UT*-scores higher than 65 were rarely encountered in the patients with schizophrenia. Although the patients with schizophrenia differed significantly from the healthy controls, most patients scored 60 or lower, indicating near normal scores. Finally, the presence of demoralization could be demonstrated in both patient groups and this should be considered as an important and underestimated issue in chronic psychiatric illness, especially in depression.

Significant differences between the three groups were found on both the Clinical and RC Scales, as expected. Our analysis demonstrated that among the 22 scales that were the primary focus of the study, nine Clinical (F, K, 1-Hs, 2-D, 3-Hy, 4-Pd, 7-Pt, 8-Sc, and 0-Si), and five RC Scales (RCd, RC1, RC2, RC3, and RC7) were able to differentiate the depression and schizophrenia patient groups. The differences found were generally consistent with those found in previous literature: 2-D, 7-Pt, 9-Ma (Ben-Porath et al., 1991; Munley et al., 1997), 4-Pd, and 0-Si (Munley et al., 1997), with the exception of 9-Ma. Eleven scales differentiated patients with schizophrenia from healthy controls, with L, F, 2-D, 3-Hy, 4-Pd, 6-Pa, 7-Pt, 8-Sc, RCd, RC2, and RC8 were higher in the schizophrenia group. Seventeen scales differentiated patients with a depression from healthy controls, with the depression group scoring higher on F, 1-Hs, 2-D, 3-Hy, 4-Pd, 6-Pa, 7-Pt, 8-Sc, 0-Si, and lower on K. Moreover, the patients with depression scored higher than the healthy control group on RCd, RC1, RC2, RC3, RC6, RC7, and RC8.

All in all, the MMPI-2 was found to differentiate between the three groups, but was better able to differentiate patients with long-term depression from healthy controls than to differentiate patients with long-term schizophrenia from the controls. The generally higher scale scores in the depression group are in line with our hypothesis, and the scores of the schizophrenia group were mostly lower than for the depression group, also as expected. The finding that the MMPI-2 scores for the schizophrenia group were mostly within the normal range (*UT*-scores < 65) was unexpected. More precisely, percentages of individuals scoring below the threshold of 65 on the various Clinical and RC Scales, range between 44% up to 96% in the patients with schizophrenia (see also Table 2 and Table 3 for the percentages of

patients that scored > 65). Note that it is generally accepted that if the highest *UT*-scores of a MMPI-2 profile are < 65, patients seem to function reasonably well. Mean scores falling < 65 are considered within the normal range, whereas a meaningful clinical interpretation may begin with scores > 60 (Butcher et al., 2001). Bearing in mind that the MMPI-2 is a measure of the individual's level of emotional adjustment (Groth-Marnat, 2009), the results of the present study are in agreement with earlier findings that patients with schizophrenia only slightly differ from healthy controls in their emotional reactions and evaluations (e.g., Hempel et al., 2005; Herbener et al., 2008; Schlenker et al., 1995). It is important to note, however, that the MMPI-2 is not a diagnostic tool like, for instance, the PANSS (Kay et al., 1987) that has the sole goal to tap positive and negative symptoms. On the MMPI-2, patients with schizophrenia seem to display a broad variety of symptoms (Bagby et al., 1997); therefore, elevations on several scales are associated with the possible presence of schizophrenia. The MMPI-2 does not provide the same profile for each patient with schizophrenia and therefore, some individual variance is possible (Bagby et al., 1997).

It appears that patients with long-term schizophrenia report less dysfunction than might be assumed in patients considered to have such a disabling illness. Considering that the MMPI-2 is based on self-report, the results indicate that our schizophrenia patients consider or experience themselves to be roughly within the normal range. Scant research has focused on the relatively "normal" scores on clinical tests that often arise in patients in whom schizophrenia has been manifest for many years. Profiles and scores on different psychological tests and questionnaires that fall within the normal range are a phenomenon that (a) may simply point towards adequate functioning (Harding, Brooks, Ashikaga, Strauss, & Breier, 1987), (b) hint at poor suitability of the test used for the group under research (Bromet et al., 2005); with respect to the MMPI-2, for instance, one could think of the possible underreporting of the negative symptoms on the test, (c) suggest that the disorder might be emotionally distressing but not sufficiently so to lead to grossly elevated scores (Graham, 2012), or (d) indicate that the effects of chronic disease itself influence test results, such as in patients with Korsakoff syndrome (e.g., Egger, Wester, de Mey, & Derksen, 2002). A profound difference between patients' self-reported and their actual level of functioning may occur (Sabbag et al., 2012), whereby self-reported functioning is influenced by the chronic psychiatric illness, causing patients to view their functioning as relatively normal or to overestimate their actual functioning. Reasons for this may be that schizophrenia is characterized by a prodromal phase, in which symptoms develop slowly and cumulatively until the point at which the disorder becomes apparent (Bäuml et al., 2005). Patients may have adapted to their symptoms, evaluate them as normal and therefore do not feel disturbed by them. It has been shown that patients with schizophrenia and good insight feel more depressed because they have a good understanding and are more aware of the limitations due to their disorder (Karow & Pajonk, 2006). Patients with schizophrenia in our sample might not properly evaluate the seriousness of their disorder.

A second reason (in addition to chronicity) for the flat profiles characterizing our schizophrenia sample may be the type of medication. Antipsychotic drugs may cause

patients to be less bothered by their symptoms or experience fewer of them (Rossell, Coakes, Shapleske, Woodruff, & David, 2003), yielding lower scores. A larger sample of patients that were more comparable when it comes to medication might have been able to shed some light on the putative role of the type of medication in relation to the flat profiles. It is therefore suggested that future research will use a larger group with systematic variation in the type of medication.

The RC Demoralization scale (RCd) was significantly higher in the depression group than in the other two groups. The patients with schizophrenia also scored significantly higher than the healthy control group. Taken together, these results show that the effect of demoralization is larger for both patient groups as compared to the healthy controls. On the other hand, our results might be partly explained by the fact that the RCd measure of demoralization is essentially a congener of the Depression content scale. In previous studies, high correlations between RCd and Depression as high as .95 have been found (Nichols, 2006; Tellegen & Ben-Porath, 2008/2011), thereby sharing virtually all of their reliable variance.

Patients with a depression scored higher than their healthy counterparts on all Clinical and RC Scales, confirming our hypothesis that patients with depression will score high on both sets of scales. The scores of the healthy controls were in the lower normal range. The differences between patients with depression and healthy controls were smaller on the RC- than on the Clinical Scales (one scale: RC4, was not significant, but Clinical Scale 4-Pd was significant). While this would suggest that demoralization has a large effect on many aspects of psychopathology and personality in this group, it needs further study as well as comparison with the effect of the aforementioned general psychopathology or 'first' factor. Demoralization did not influence the tendency towards antisocial behavior in these patients.

One limitation of our data is the relatively small sample size (Streiner, 1990), which was due to recruiting difficulties (Patel, Doku, & Tennakoon, 2003). In future research, a larger sample size may enhance generalizability of the results (Mudano et al., 2013).

To conclude, the main finding of our study is that, with regard to psychopathology and personality self report, it is hard to differentiate long-term patients with schizophrenia from healthy controls, considering their flat profiles and low individual *UT*-scores. The current study suggests clinical alertness in cases with relatively low clinical scale scores in combination with slightly elevated RCd scores. These findings are rather unexpected, and in sharp contrast to what the MMPI-2 can do with respect to differentiating patients with long-term depression from healthy controls. Secondly, demoralization may play an important role in both patient groups. This might be due to the patients' perception of their own symptoms and their long-term illness. We conclude that long-term patients with depression show impaired functioning and high demoralization, while long-term patients with schizophrenia surprisingly show near normal functioning and less demoralization. Since the self report of patients with chronic psychiatric illness may markedly contrast with their daily functioning, the clinician is prone to incorrect judgments on health status, possibly resulting from underestimation of actual psychopathology. A special awareness for this phenomenon

should be developed among clinicians and, where possible, be incorporated in the relevant residency programs.

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Chapter 3

The Munich Parasomnia Screening in psychiatry

Based on:

Bosch, P., van Luijtelaar, G., Groetelaers, L., Van den Noort, M., Lim, S., Egger, J., & Coenen, A. (2012). The Munich Parasomnia Screening in Psychiatry. *Somnology - Sleep Research and Sleep Medicine, 16*(4), 257–262. doi:10.1007/s11818-012-0587-4

Abstract

Background The aim was to investigate the subjective experience of parasomnias and other nocturnal behaviors in depression and schizophrenia.

Materials and Methods Using the Munich Parasomnia Screening (MUPS), 21 parasomnias and other nocturnal behaviors were assessed in 85 participants; 27 were patients with depression, 29 were patients with schizophrenia and 29 were healthy control participants.

Results A significant group-difference was found for: hypnagogic hallucinations, sleep-related bruxism, sleep talking, sleep-related abnormal swallowing, leg cramps, nightmares, pavor nocturnus, confusional arousals, and sleep paralysis. Highest scores in depression point towards a correlation between depression and the prevalence of parasomnias. Parasomnias did not cluster according to their occurrence.

Conclusion Although all patients with depression had experienced nocturnal behaviors, none had a previous parasomnia diagnosis or was treated accordingly. 97.6% of all participants had experienced nocturnal behaviors. Prevalence in depression was highest, asking for more clinical awareness and thereby better future treatments and outcomes. A screening instrument like the MUPS is essential in filtering out patients who seem to experience parasomnias.

Introduction

Although there is ample evidence for a correlation between psychiatric disorders and various sleep disorders (Buysse et al., 1994; Sateia, 2009), much is still unclear about parasomnias and their prevalence in depression and schizophrenia (e.g., Kerkhof, 2006).

According to the International Classification of Sleep Disorders Version 2 (ICSD-2) (American Academy of Sleep Medicine, 2005), parasomnias can be divided into three categories, i.e., 'partial arousals during non-REM sleep', 'REM-sleep parasomnias' and 'other parasomnias'. The first category consists of: sleep walking, confusional arousals and pavor nocturnus (sleep terror), usually occurring during sudden awakenings out of 'slow wave sleep' (SWS) (Broughton, 2000). The second category consists of 'REM-sleep behavior disorder' (RSBD), nightmares and sleep paralyses; RSBD occurs during REM sleep, while nightmares and sleep paralyses mostly occur during the shift from REM sleep to wakefulness. The third category consists of parasomnias that do not specifically present themselves during a certain stage: nocturnal enuresis or bedwetting, sleep related dissociative disorder, 'exploding head syndrome', sleep related eating disorder (SRED), cathathrenia or nocturnal expiratory groaning, and hypnagogic hallucinations (Mason & Pack, 2007).

The subjective experience of parasomnias in depression, schizophrenia and healthy controls, is the focus of the present study. Both psychiatric disorders are characterized by marked disturbances of sleep (Costa e Silva, 2006; Kerkhof, 2006; Lam, Fong, Ho, Yu, & Wing, 2008; Sateia, 2009). Because parasomnias and other sleep disorders often co-occur (e.g., Kerkhof, 2006; Lam et al., 2008), a co-morbidity of different types of sleep disorders and psychopathology is expected. However, most studies on the correlation between nocturnal behavior and psychopathology describe few parasomnias only. From those studies, especially sleepwalking (Lam et al., 2008; Ohayon, Guilleminault, & Priest, 1999), sleep paralysis (Rotenberg et al., 2002; Van Os & Kapur, 2009), RSBD, and SRED (Lam et al., 2008) seem to be associated with depression. In schizophrenia spectrum disorders, nightmares are frequently reported (Hublin, Kaprio, Partinen, & Koskenvuo, 1999; Levin & Fireman, 2002). In order to detect and quantify parasomnias, the Munich Parasomnia Screening (MUPS) (Fulda et al., 2008) was used. Since sleep walking and pavor nocturnus have been found to appear together (Oudiette et al., 2009), it is hypothesized that parasomnias out of the same group co-occur. Patients with a depression spend more time in REM sleep (Rotenberg et al., 2002), and because REM sleep parasomnias therefore have more opportunities to occur, it is expected that they will occur more in this group. Moreover, depression is a risk factor for the occurrence of parasomnias. This view is based on previous research (Lam et al., 2008), describing that sleep walking, SRED and RSBD occur more often in patients with depression than in those with schizophrenia. Partial arousals to non-REM sleep are known to occur more in childhood and in some families hat have a (genetic) history of partial arousals. Moreover, they may be facilitated by factors that deepen sleep (Markov, Jaffe, & Doghramji, 2006) Schizophrenia is characterized by continuing larger percentages of deep non-REM

sleep (Keshavan et al., 1998). Because parasomnias belonging to this sleep stage have more opportunities to occur and since more deeper sleep may facilitate the occurrence of partial arousals to non-REM sleep, this group may show more partial arousals of non-REM sleep than the other groups (Broughton, 2000) and more partial arousals of non-REM sleep than REM sleep parasomnias.

Method

Participants

Eighty-five participants (36 men and 49 women, age *M* = 42.95, *SD* = 10.66) took part in the study, of which 27 were outpatients with depression (6 men and 21 women, age *M* = 48.00, *SD* = 9.56), 29 were outpatients with schizophrenia (15 men and 14 women, age *M* = 41.48, *SD* = 9.82), and the control group consisted of 29 healthy participants (15 men and 14 women, age *M* =39.72, *SD* = 11.06). Recruiting limitations resulted in a higher mean age (schizophrenia ($p < .05$) and control ($p < .01$)) and more women (schizophrenia ($p < .05$) and control ($p < .05$)) in the group with depression.

All patients (age 18-64, diagnosed according to the ICD-10 (World Health Organization, 1992)) participated voluntarily and signed an informed consent after being asked by their therapist in the LVR-Klinik Bedburg-Hau in Germany. The study was approved by the ethical committee, and performed in accordance with the Declaration of Helsinki (World Medical Organization, 2008).

Exclusion criteria were substance abuse and/or epilepsy and other neurological conditions. For the control group, the exclusion criteria were the presence of neurological- or psychiatric disorders.

Material

The MUPS (Fulda et al., 2008) is a self-evaluation questionnaire that assesses 21 parasomnias and other nocturnal behaviors (see Table 1). With seven possible answering categories, the lifelong frequency of appearance is assessed for every item. The main question is ‘How often do you experience the following behaviors?’. The answering categories are ‘never’, ‘was observed _ years ago, but not anymore’, ‘very seldom – less than once a year’, ‘seldom – once or several times a year’, ‘sometimes – once or several times a month’, ‘frequently – once or several times a week’ and ‘very frequently – every or almost every night’. For reasons of analyses, the qualitative MUPS was scored quantitatively using a seven point scale (0 = never, 1 = years ago, 2 = very rarely, 3 = rarely, 4 = sometimes, 5 = often, 6 = very often). Every score was calculated per item and per group.

All but two of the 21 questions were shown (Fulda et al., 2008) to have a sensitivity of equal to or above 90%, and all items have a specificity of more than 80%, 19 of 21 items even above 90%. It was found to be a valid and easy to use instrument in the recognition of nocturnal behaviors (Wetter & Schenck, 2008).

Procedure

Due to the fact that the dataset is not normally distributed, the Kruskal Wallis Test was conducted with $\alpha = .05$ in order to evaluate possible group differences. The group (depression, schizophrenia, control) was used as grouping variable, with the 21 items of the MUPS as dependent variable. The Mann-Whitney-U Test was used as follow-up. Moreover, factor analyses on the MUPS items were conducted using promax rotation.

Results

Comparison of Nocturnal Behavior

It was found that 97.6% of the participants had experienced parasomnias and other nocturnal behaviors (see Table 1.)

Table 1.

Overview of the scores on the different parasomnias per experimental group

	Parasomnias[a]																					
Group[b]	Score[c]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
C	0	10	21	28	27	27	25	8	22	11	28	20	26	8	26	20	29	27	28	24	21	25
C	1	4	0	0	0	0	0	3	3	1	0	0	2	3	0	0	0	0	0	2	1	1
C	2	3	1	0	0	1	1	6	0	5	0	2	1	6	2	4	0	1	1	3	5	2
C	3	5	5	0	2	1	2	11	1	6	0	2	0	8	0	4	0	1	0	0	0	1
C	4	4	2	0	0	0	0	1	2	5	1	3	0	3	1	0	0	0	0	0	2	0
C	5	3	0	0	0	0	0	0	0	1	0	2	0	1	0	1	0	0	0	0	0	0
C	6	0	0	1	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
D	0	8	14	21	20	17	20	4	12	8	18	17	26	2	13	15	27	17	20	21	18	8
D	1	2	2	1	0	2	0	5	3	1	2	1	0	2	2	1	0	0	1	2	1	2
D	2	1	2	1	3	4	0	3	3	7	1	1	0	5	3	5	0	3	2	2	4	1
D	3	7	1	2	1	1	3	8	2	5	1	4	0	5	5	1	0	2	2	1	0	7

Table Continues

	Parasomnias[a]																					
D	4	6	5	1	2	1	3	5	3	2	1	2	1	5	1	1	0	3	1	1	1	6
D	5	2	2	0	1	1	0	2	2	0	3	1	0	4	3	1	0	2	1	0	1	2
D	6	1	1	1	0	1	1	0	2	4	1	1	0	3	0	3	0	0	0	0	2	1
S	0	13	23	22	25	22	21	10	22	18	21	24	22	4	22	14	27	19	27	24	24	24
S	1	3	2	2	0	2	2	8	2	5	0	0	4	2	0	1	0	1	0	3	3	3
S	2	4	1	1	2	2	3	7	1	1	1	3	2	6	4	2	2	5	2	0	0	2
S	3	2	0	1	1	2	1	2	1	1	2	2	0	7	2	3	0	1	0	2	1	0
S	4	5	0	0	0	1	1	1	0	2	5	0	0	5	1	6	0	3	0	0	1	0
S	5	1	1	2	1	0	1	1	2	1	0	0	0	4	0	2	0	0	0	0	0	0
S	6	1	2	1	0	0	0	0	1	1	0	0	1	1	0	1	0	0	0	0	0	0

[a]: 1 = Hypnic jerks, 2 = Rhythmic feet movements, 3 = Rhythmic movement disorder, 4 = Exploding head syndrome, 5 = Hypnagogic hallucinations, 6 = Periodic leg movements, 7 = Nocturnal leg cramps, 8 = Sleep-related bruxism, 9 = Sleep talking, 10 = Sleep-related abnormal swallowing, 11 = Nocturnal groaning, 12 = Nocturnal enuresis, 13 = Nightmares, 14 = Pavor nocturnus, 15 = Nocturnal eating, 16 = Sleep related eating disorder, 17 = Confusional arousals, 18 = Sleep paralysis, 19 = Sleep walking, 20 = Violent behavior, 21 = RSBD.

[b]: C = control group, D = group with depression, S = group with schizophrenia.

[c]: 0 = never, 1 = years ago, 2 = very rarely, 3 = rarely, 4 = sometimes, 5 = often, 6 = very often.

A descriptive analysis was made for all variables (see Table 2). Kruskal-Wallis tests were conducted to evaluate differences among the three groups on the 21 items of the MUPS. For the following items, tests were corrected for tied ranks and found to be significant. A strong effect was found for pavor nocturnus $\chi^2(2, N = 85)= 12.64$, $p = .00$, $\eta^2 = .15$ and a medium effect for: hypnagogic hallucinations $\chi^2(2, N = 85) = 7.24$, $p = .02$, $\eta^2 = .09$; nocturnal leg cramps $\chi^2(2, N = 85) = 9.55$, $p = .01$, $\eta^2 = .09$; sleep-related bruxism $\chi^2(2, N = 85) = 8.08$, $p = .02$, $\eta^2 =.10$; sleep talking $\chi^2(2, N = 85) = 7.52$, $p = .02$, $\eta^2 = .09$; sleep-related abnormal swallowing $\chi^2(2, N = 85) = 8.29$, $p = .02$, $\eta^2 = .10$; nightmares $\chi^2(2, N = 85) = 8.83$, $p = .01$, $\eta^2 = .11$; confusional arousals $\chi^2(2, N = 85) = 8.53$, $p = .01$,$\eta^2 =.10$ and sleep paralysis $\chi^2(2, N = 85) = 8.10$, $p = .02$, $\eta^2 = .10$.

Subsequently, post hoc Mann-Whitney-U tests with Bonferroni correction ($p < .016$), were conducted for all significant items. The results show that the group with depression scored highest on all nocturnal behaviors that differed significantly between the groups. The results show a significant difference between the group with depression and the control group for the items: hypnagogic hallucinations $z = -2.68$, $p = .007$, sleep-related bruxism z = -2.44, $p = .015$, sleep-related abnormal swallowing $z = -2.87$, $p = .004$, nightmares $z = -2.87$, $p = .004$, pavor nocturnus $z = -3.35$, $p = .00$, confusional arousals $z = -2.80$, $p < .01$, sleep paralyses z = -2.41, $p = .001$.

On sleep talking $z = -2.67$, $p = .008$, sleep paralyses $z = -2.41$, $p = .016$ nocturnal leg cramps $z = -2.92$, $p = .004$, sleep-related bruxism $z = -2.29$, $p = .015$, and pavor nocturnus $z = -2.23$, $p = .001$, the group with schizophrenia achieved the lowest scores, that were significantly different from the group with depression, but not from the control group.

On sleep-related abnormal swallowing $z = -2.47$, $p = .013$, and confusional arousals z = -2.55, $p = .011$ the group with schizophrenia scored significantly higher than the control group only.

Table 2.
Mean Ranks on the Items per Nocturnal Behavior

Item	Occurrence	Parasomnia/Nocturnal behavior	Depression	Schizophrenia	Control
13.	REM sleep parasomnias	Nightmares	51.91[a]	44.83	32.88
18.	REM sleep parasomnias	Sleep paralysis	49.19[a,b]	40.83	39.41
21.	REM sleep parasomnias	RSBD	46.59	41.79	40.86
14.	Partial arousals during non-REM sleep	Pavor nocturnus	53.52[a,b]	40.93	35.28
17.	Partial arousals during non-REM sleep	Confusional arousals	48.61[a]	46.00[a]	34.78
19.	Partial arousals during non-REM sleep	Sleep walking	44.70	42.24	42.17
4.	Other parasomnias	Exploding head syndrome	47.56	42.29	39.47
5.	Other parasomnias	Hypnagogic hallucinations	49.39[a]	43.57	36.48
11.	Other parasomnias	Nocturnal groaning	46.72	38.09	44.45
12.	Other parasomnias	Nocturnal enuresis	39.22	47.72	41.79
15.	Other parasomnias	Nocturnal eating	43.74	48.29	37.02
16.	Other parasomnias	Sleep related eating disorder	42.00	44.93	42.00
1.	Other sleep related nocturnal behaviors	Hypnic jerks	48.09	38.62	42.64
2.	Other sleep related nocturnal behaviors	Rhythmic feet movements	50.31	38.38	40.81
3.	Other sleep related nocturnal behaviors	Rhythmic movement disorder	45.35	46.16	37.66
6.	Other sleep related nocturnal behaviors	Periodic leg movements	45.28	44.45	39.43
7.	Other sleep related nocturnal behaviors	Nocturnal leg cramps	52.94[b]	33.07	43.67
8.	Other sleep related nocturnal behaviors	Sleep-related bruxism	52.41[a,b]	38.88	38.36
9.	Other sleep related nocturnal behaviors	Sleep talking	49.91[b]	33.52	46.05
10.	Other sleep related nocturnal behaviors	Sleep-related abnormal swallowing	48.31[a]	45.53[a]	35.52
20.	Other sleep related nocturnal behaviors	Violent behavior	46.91	38.78	43.59

According to the Mann Whithney U tests: [a] Mean rank is significantly different ($p < .05$) from control. [b] Mean rank is significantly different ($p < .05$) from schizophrenia.

Parasomnia Categories

In order to establish whether the parasomnias within one category (the three categories being: 'partial arousals during non-REM sleep', 'REM-sleep parasomnias' and 'other parasomnias') are indeed associated, a Spearman's Rank Order correlation was run to

determine the relationship between parasomnias in one category. If parasomnias would cluster according to their appearance, that would justify categorization according to these three categories. Only pavor nocturnus and confusional arousals were correlated ($r_S(83) = .305$, $p < .01$) in the partial arousal from non-REM sleep category, while sleepwalking was not significantly correlated to the other two.

In the REM sleep parasomnia category, both nightmares and sleep paralysis ($r_S(83) = .272$, $p < .05$) as well as nightmares and RSBD ($r_S(83) = .222$, $p < .05$) were correlated, whereas the correlation between sleep paralysis and RSBD was not significant.

Moreover, most parasomnias from one category also correlated with parasomnias from other categories. Significant correlations were found between pavor nocturnus and all three REM sleep parasomnias: nightmares ($r_S(83) = .379$, $p < .01$), sleep paralysis ($r_S(83) = .336$, $p < .01$) and RSBD ($r_S(83) = .256$, $p < .05$), and moreover, between confusional arousals and nightmares ($r_S(83) = .305$, $p < .05$) and between sleep walking and RSBD ($r_S(83) = .292$, $p < .01$).

The factor analysis extracted eight factors and its structure was not compatible with the categories suggested by the ICSD-2 (American Academy of Sleep Medicine, 2005), because two of the three partial arousals during non-REM sleep (pavor nocturnus and confusional arousals) load high on the same factor, but the third one (sleep walking) does not. The three REM sleep parasomnias (nightmares, sleep paralysis and RSBD) all loaded high on three different factors (see Table 3). Moreover, it was difficult to interpret the eight factors, because the items that load high on the same factor did not seem to have anything in common.

Table 3.
Factorloads of the Items after Factor Analysis with Maximum Likelihood and Promax Rotation

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6	Factor 7	Factor 8
Violent behavior	.987							
RSBD	.664							
Sleep related groaning	.474							
Sleep talking	.305							
Pavor nocturnes		.770						
Confusional arousals		.685						
Sleep-related abnormal swallowing		.488						
Rhythmic movement disorder		.301						
Exploding head syndrome			1.039					
Hypnagogic hallucinations			.447	.371				
Hypnic jerks				.908				
Rhythmic feet movements				.508				
Sleepwalking					.995			
Sleep-related eating disorder								
Nightmares						.943		
Sleep paralysis								
Nocturnal leg cramps							-.906	
Nocturnal enuresis							.372	
Nocturnal eating								
Periodic leg movements								.588
Sleep-related bruxism								.564

Continuing factor analyses until every item loads higher than .30 on one factor and thereby excluding the items that load high on no factor or that load high on more factors at the same time, resulted in 12 items that were distributed along five factors. But even then parasomnia from one category load high on different factors and parasomnia from different categories load high on the same factor.

Category Differences in Schizophrenia

A number of REM sleep parasomnias appear more often than partial arousals during non-REM sleep in the group with schizophrenia $\chi^2(3) = 43.93$, $p = 0.000$. A post-hoc Mann Whitney U Test with Bonferroni correction was applied, resulting in a significance level set at $p < 0.008$. It was found that the REM sleep parasomnia nightmares appeared more than the three arousals during non-REM sleep: pavor nocturnus ($Z = -4.033$, $p = .000$), confusional arousals ($Z = -3.758$, $p = .000$), and sleepwalking ($Z = -4.393$, $p = .000$). On the other hand, one of the other REM sleep parasomnias; sleep paralysis was found significantly less than the non-REM sleep parasomnia; confusional arousals ($Z = -2.176$, $p = .007$).

Differences between the Groups

The distribution of men and women was not equal. Analysis of covariance showed that gender influenced only sleep related bruxism (which was significantly higher in the depression group, and therefore in the group with more women). A second difference between the groups was that age was also higher in the group with depression. Analyses of

covariance, however, showed that age was only a contributing factor in explaining sleep related abnormal swallowing (which occurred more in the older group), it did not contribute to any of the other results.

Discussion

Of the total sample, 97.6% had experienced nocturnal behaviors; the parasomnias that occurred the most by far were nightmares, followed by hypnic jerks, nocturnal leg cramps, sleep talking, and finally nocturnal eating. Patients with a depression suffered the most.

The assumption that parasomnias would correlate within their category and that there would be specific differences in prevalence between the groups with depression and schizophrenia, was partially confirmed. Among the three partial arousals during non-REM sleep, pavor nocturnus and confusional arousals were correlated, while sleepwalking and pavor nocturnus merely showed a marginally significant correlation. These findings are not in line with Oudiette et al. (2009), who found that sleepwalking and pavor nocturnus co-occurred. Among the three REM sleep parasomnias significant correlations were found between nightmares and sleep paralyses and between nightmares and RSBD, but not between sleep paralyses and RSBD. These findings partly confirm the theory that parasomnias from one category correlate and co-occur more often. Moreover, significant correlations were found with parasomnias that belong to another category. Pavor nocturnus was found to be significantly correlated to nightmares and RSBD, confusional arousals was correlated to nightmares and sleepwalking was related to RSBD. Also by means of a factor analysis only few correlations between parasomnias belonging to the same category were found.

Factor analysis resulted in eight factors that do not have anything in common with the ICSD-2 (American Academy of Sleep Medicine, 2005). Moreover, they do not seem relevant for clinical practice, and therefore it would not be helpful to restructure the MUPS, creating a score system for the different factors. It seems more practical to keep the MUPS the way it is now, providing a clear overview of the subjective presence of parasomnias within two A4 pages.

The expectation that having a depression is a risk factor for developing parasomnias is strongly affirmed in accordance with Lam et al. (2008). From the 21 items, nine showed a significant difference between the depression, schizophrenia and the healthy control group. Two of the items belong to the arousals during non-REM sleep, two belong to the REM sleep parasomnias, one to other parasomnias, and four to other nocturnal behaviors. All occur most in the group with depression, which discriminates significantly from the control group on 7 and from that with schizophrenia on 5 nocturnal behaviors. On the other hand, the group with schizophrenia scores significantly higher than the control group on two items only.

Parasomnias appeared more often in people with psychiatric problems than in healthy people, confirming earlier findings (e.g., Vgontzas & Kales, 1999). This has clinical

relevance because sleep problems in general (Shneerson, 2000) and particularly parasomnia (Lam et al., 2008), are often deficiently diagnosed or treated. Remarkably, none of the 27 patients with a depression was previously diagnosed with parasomnias or nocturnal behaviors, illustrating the extreme under-diagnoses. This finding illustrates that the MUPS is able to function as a screening instrument, because it illustrates patient's subjective opinion of possible parasomnias that they have experienced. They may not mention these parasomnias when they visit their psychiatrist and therefore, these symptoms remain unnoticed. To optimize treatment, in sharp contrast to current practice, these patients should be screened with an instrument like the MUPS.

Perhaps patients with schizophrenia are less aware of the appearance of parasomnias than the other groups due to the use of antipsychotic medication (Van Os & Kapur, 2009). In future research proxy ratings/observations might be used to shed more light on this subject. Moreover, in this study, the subjective patient's experience of parasomnias was investigated; however, in future research it would be interesting to investigate not only the subjective experience, but also the actual clinical confirmation of parasomnias and their diagnosis.

A shortcoming of this study is that the medication used by the different patients groups was not comparable in doses or sort of medication. Most patients with schizophrenia used two or more types of medication, including antipsychotics and antidepressants, whereas most patients in the group with depression used at least one antidepressant and some used additional medication. In future research more strict inclusion criteria might be used in order to have a more comparable sample and to exclude influence by the medication.

A second shortcoming of our study is the size of the experimental groups. Owing to recruitment difficulties and strict ethical limitations, it was not possible to include more patients in the study.

To conclude, the development and standardized use of tests like the MUPS that focus on sleep disorders seems to be a simple, cheap, and timesaving method to avoid further under-diagnoses of parasomnias and other nocturnal behaviors. More awareness might lead to better treatments and thereby better treatment outcomes.

Conclusion for clinical practice

Parasomnias and other nocturnal behaviors occur often, and patients with depression in particular are at risk. Tests like the MUPS are a great method with which to increase awareness of parasomnia, thereby helping to develop better treatments and treatment outcomes.

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Chapter 4

Sleep ameliorating effects of acupuncture in a psychiatric population

Based on:

Bosch, P., van Luijtelaar, G., van den Noort, M., Lim, S., Egger, J., & Coenen, A. (2013). Sleep ameliorating effects of acupuncture in a psychiatric population. *Evidence-Based Complementary and Alternative Medicine*, 969032. doi:10.1155/2013/969032

Abstract

The interest of psychiatric patients for complementary medicine, such as acupuncture, is stable, but effect studies in psychiatry remain scarce. In this pilot study, the effects of 3 months of acupuncture treatment on sleep were evaluated and compared between a group of patients with schizophrenia (*n* = 16) and a group with depression (*n* = 16). Healthy controls were included in order to establish reference values (*n* = 8). Patients with schizophrenia and depression were randomly assigned to either a waiting list or a treatment condition. The Pittsburgh Sleep Quality Inventory was completed before and after the acupuncture treatment (individualized and according to Traditional Chinese Medicine principles) or the waiting list condition. Both acupuncture groups showed significant lower scores on the sleep inventory, which was not the case for the waiting list condition. Moreover, it was found that the effectiveness of the acupuncture treatment was higher in the patients with schizophrenia than in the patients with depression. Acupuncture seems able to improve sleep in this convenient sample of patients with long lasting psychiatric problems and may be a suitable and cost-effective add-on treatment for this group, particularly if conducted group-wise.

1. Introduction

Interest in complementary and alternative medicine (CAM), such as acupuncture, has increased in popularity in Western societies in the last part of the twentieth century and there has been a continued interest ever since (Harris, Cooper, Relton, & Thomas, 2012). The use of CAM includes its application in psychiatric patients (Elkins, Rajab, & Marcus, 2005). Two large groups that need long-term treatment are patients with depression and patients with schizophrenia. Besides the typical depressive or positive and negative symptoms, their disorders are characterized by marked disturbances of sleep (Buysse et al., 2008; Chouinard, Poulin, Stip, & Godbout, 2004; Cukrowicz et al., 2006; Monti & Monti, 2004; Monti & Monti, 2005; Taylor, Lichstein, Durrence, Reidel, & Bush, 2005). Patients with schizophrenia show increased sleep latency, decreased total sleep time, and decreased sleep efficiency (Chouinard et al., 2004; Monti & Monti, 2004; Monti & Monti, 2005). A bidirectional relationship between insomnia and depressive symptoms in patients with depression is described (Buysse et al., 2008; Cukrowicz et al., 2006; Taylor et al., 2005). Sleep problems such as increased sleep latency, awakenings in the night or early in the morning with an incapability to go back to sleep, and decreased sleep efficiency are typical symptoms of depression; whereas hypersomnia and dream-disturbances are also often reported. The sleep disorders appear to maintain or even deteriorate the mood disorder (Stein, Kupfer, & Schatzberg, 2006).

In Western psychiatry, a growing consumption of antipsychotic (Lertxundi, Echaburu, & Palacios, 2012) and antidepressant drugs (Pratt, Brody, & Gu, 2011) can be seen. Antipsychotic application is seen as the cornerstone in therapy for patients with schizophrenia (Tandon, Nasrallah, & Keshavan, 2010); whereas due to their positive effects, antidepressants have found their place in the clinical guidelines for the treatment of, for instance, patients with depression (NICE Depression, 2010). Despite these clinical successes, a problem with pharmaceutical therapies (Ascher-Svanum, Peng, Faries, Montgomery, & Haddad, 2009), like any other therapy, is that they are subject to patient non-adherence and declining patient compliance (Bodén, Brandt, Kieler, Andersen, & Reutfors, 2011; Goff, Hill, & Freudenreich, 2010).

Previous research has shown that adherence to treatment correlates negatively with sleep disturbance and depression (Phillips et al., 2005). It seems that a lack of contact with this patient group makes it difficult to engage in a therapeutic relationship or to prescribe and monitor medication effectively. The medicines used to treat these conditions often cause drowsiness (Seeman, 2012). Patients are therefore often advised to take them at night which cause problems with sleep (e.g. excessive dreaming and increase in total sleep time in patients with schizophrenia (Monti & Monti, 2004)) even though taking them at night minimizes daytime drowsiness. Moreover, tiredness, drowsiness and poor sleep interferes with the patient's ability to engage with therapeutic services because they are too tired, unmotivated and they do not see the point or do not want to take medicines that cause such adverse effects. Presumably, these are not the only factors that are of importance, but they

seem highly relevant in patient groups that suffer from depression, as well as those that suffer from schizophrenia, since both diseases are prone to sleep disorders.

Acupuncture is part of Traditional Chinese Medicine (TCM), which in itself is a form of CAM that is based on thousands of years of practice (Kavoussi, 2007). One of the features of the TCM approach is the individualization of treatment, which relies on a symptom-based diagnostic process (Zhang et al., 2005). TCM diagnoses are based on clinical symptoms and signs that are completely discerned by the oriental medical practitioner (Zhang et al., 2005).

Recent years have seen an increase in trials on particularly depression and acupuncture (Yeung, Ameral, Chuzi, Fava, & Mischoulon, 2011; Lyons, van der Watt, Shen, & Janca, 2012; Zhang, Yang, & Zhong, 2009). Various reviews, however, have concluded that evidence for the effects of acupuncture on depression still remains preliminary (Leo & Ligot, 2007; Schroer & Adamson, 2011; Wang et al., 2008). In particular methodological problems, such as different techniques (electro-, manual-, or laser acupuncture), various control groups and study designs, limit the generalization of the results (Bosch, Ausfeld, & van den Noort, 2008; Yeung et al., 2011). Although efforts have been made to standardize and optimize research and the way it is reported, further research is warranted (Leo & Ligot, 2007; MacPherson et al., 2010).

Even less research with acupuncture has been conducted on schizophrenia. Some literature research (Bosch & van den Noort, 2008; Rathbone & Xia, 2005) indicates that more research is necessary to draw firm conclusions on acupuncture's effectiveness in the treatment of schizophrenia. Moreover, even though some research was reported (Lee, Shin, Ronan, & Ernst, 2009; Ronan, Harbinson, MacInnes, Lewis, & Robinson, 2010), hinting in the direction of effectiveness and thereby providing the basis for future research, the existing research remains preliminary.

Acupuncture may be beneficial in the treatment of sleep disorders (Peterson, 2002). It can be used alone or combined with other interventions, since no interactions were found to date and adverse events related to treatment seem sufficiently controllable by providing thorough training (Vincent, 2001). Although some research has been conducted on acupuncture and sleep disorders (Bosco Guerreiro da Silva, Uchiyama Nakamura, Cordeiro, & Kulay, 2005; Freire et al., 2007; Montakab, 1999; Spence et al., 2004), results are still tentative, particularly in patients with psychiatric disorders. Results call for research in a group, in which symptoms are prominent, since acupuncture's effectiveness is thought to rely on its homeostatic actions, striving to return the body to its normal physiological state. Therefore, it is thought that acupuncture has more effects on patients that experience serious problems than on healthy participants or patients with only mild symptoms (Bosch & van den Noort, 2008).

This pilot study evaluates and compares the effects of acupuncture on the subjective quality of sleep in long-term patients with schizophrenia and patients with depression. It is a pragmatic trial, and a first start to conduct research in an integrative treatment setting in which psychiatric treatment and TCM are combined.

2. Materials and Methods

2.1. Participants. In total the convenient sample consisted of 40 participants (13 men, 27 women). 16 of them (10 women, 6 men, mean age was 44.25 years, *SD* = 2.44*)* diagnosed with schizophrenia, 16 of them (12 women, 4 men, mean age was 50.94 years, *SD* = 1.33*)* diagnosed with depression. The healthy control group consisted of 5 women and 3 men (mean age was 36.75 years, *SD* = 12.43). Mean length of illness was 13.56 years (*SD* = 1.59) for the group with schizophrenia and 5.94 years (*SD* = 1.05) for the group with depression. The randomization function in Excel was used to randomly divide the patients into a treatment and a waiting list condition. For an overview of the descriptive statistics see Table 1 and for an overview of the medication used, see Table 2.

Table 1.

Overview of the descriptive statistics of the convenient sample.

	Schizophrenia (*SD*)			Depression (*SD*)			Healthy Control (*SD*)
	Total	Waiting list	Acupuncture	Total	Waiting list	Acupuncture	Total
Men	6	3	3	4	2	2	3
Women	10	5	5	12	6	6	5
Length of illness	13.56 (1.59)	12.63 (5.90)[a]	14.50 (7.07)[a]	5.94 (1.05)	4.38 (3.54)	7.50 (4.41)	0
Age	44.25 (2.44)	42.25 (10.99)	46.25 (8.57)	50.94 (1.33)	52.88 (5.59)[b]	49.00 (4.54)	36.75 (12.43)

According to the one-way ANOVA (groups as between subjects factor) at baseline: [a] Mean is significantly different ($p < 0.05$) from the depression waiting list group. [b] Mean is significantly different ($p < 0.05$) from the healthy control group.

Table 2.

Overview of the medication used by the different groups at the start of the study.

Group	**CPZ**	**Atypical**	**Typical**	**SSRI**	**Tricyclic anti-depressives**	**SNRI and SSNRI**	**Others**
Depression and acupuncture group	Chlorprothixene in 1 patient Promethazine in 1 patient Pipamperone in 1 patient 0,33 in 1 patient	In 2 patients	In 2 patients	In 4 patients	In 3 patients	In 3 patients	In 2 patients
Depression and waitlist group	Pipamperone in 1 patient 0,33 in 1 patient	In 1 patient	In 1 patient	In 4 patients	In 2 patients	In 3 patients	In 2 patients
Schizophrenia and acupuncture group	Amisulpride + 1 in 1 patient Zotepine + 1 in 1 patient Prothipendyl + 2 in 1 patient Flupenazine + 3 in 1 patient 6 in 1 patient 4 in 1 patient 3,5 in 1 patient 1,83 in 1 patient	In 8 patients	In 3 patients	In 0 patients	In 1 patient	In 1 patient	In 4 patients

Group	CPZ	Atypical	Typical	SSRI	Tricyclic anti-depressives	SNRI and SSNRI	Others
Schizophrenia and waitlist group	Fluphenazine + 3 in 1 patient 6 in 1 patient Pipamperone + 3,17 in 1 patient 1,83 in 1 patient 1 in 1 patient Zotepine and Chlorprothixene and Melperone + 4 in 1 patient 10 in 1 patient 3,5 in 1 patient	In 8 patients	In 3 patients	In 0 patients	In 2 patients	In 0 patients	In 4 patients

CPZ (Chlorpromazine Equivalents) were calculated using published equivalencies for oral conventional (American Psychiatric Association, 1997) and atypical (Woods, 2003) antipsychotics.

SSRI = Selective Serotonin Reuptake Inhibitor, SNRI = Serotonin Norepinephrine Reuptake Inhibitor, SSNRI = Selective Serotonin Norepinephrine Reuptake Inhibitor

Recruiting limitations resulted in a higher mean age in the depression waiting list condition than in the healthy control group ($p < 0.05$). There was a poster in the entrance section and in the waiting room that gave information on the study. Moreover, potential participants (diagnosed with schizophrenia F 20.0 (paranoid schizophrenia), F20.5 (schizophrenic residuum), or depression F33.2 according to the ICD-10) (World Health Organization, 1992) were identified and approached by their therapist at the LVR-Klinik Bedburg-Hau. Patients that agreed to participate did so voluntarily and signed an informed consent form; moreover, their therapist signed for their mental ability to understand the form. The Becks Depression Inventory-II (Beck, Steer, & Brown, 1996) and Positive And Negative Symptom Scale (PANSS) (Kay, Fiszbein, & Opler, 1987) were used as inclusion criteria. The study was carried out in accordance with the Declaration of Helsinki (World Medical Organization, 2008) and was approved by the ethical committee of the Ärztekammer Nordrhein.

Participants continued with their normal psychiatric treatment, including medication, alongside acupuncture. After the project, the medical files were checked for possible changes in medication during the time of the project. Moreover, possible use of sleep medication was mentioned by the patients on the Pittsburgh Sleep Quality Inventory (PSQI). Five of the patients with schizophrenia (all in the acupuncture condition) used sleep medication beforehand. Six of the patients with depression (two in the acupuncture and four in the waiting list condition) and none of the healthy control group used sleep medication. Of the five patients in the schizophrenia and acupuncture group, one of them used Prothipendyl (80 mg daily), one used Prothipendyl (40 mg daily), one used Sifrol (0.36 mg daily) one used Amitriptyline (50 mg daily), and one used Melperone (75 mg daily). In the depression and acupuncture group one patient used Chlorprothixene (30 mg daily) and one patient Pipamperone (40 mg daily). Finally in the depression and waiting list condition group one patient used Pipamperone (40 mg daily) and three patients Zopiclone (7.5 mg daily/when needed). Probably due to the natural course of the diseases and recruitment limitations, the group of participants diagnosed with schizophrenia had been in treatment significantly longer than those with depression. There were no gender differences within and between the groups. Exclusion criteria for the patients were substance abuse and/or epilepsy and other neurological conditions. For the control group, the exclusion criteria were the presence of neurological- or psychiatric disorders.

2.2. Instruments

2.2.1. Pittsburgh Sleep Quality Inventory. The German version of the PSQI (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) was used in order to gain information on the subjective quality and quantity of sleep in the participants. With this retrospective list, conducting questions about sleep during the last four weeks, information on the number of sleep disturbances, estimation on sleep quality, sleep duration, sleep latency and sleep times, use of medication, and sleepiness during the day is being gathered. The questionnaire consists of 18 items, divided into 7 components that can be scored from 0-3. The PSQI Total Score results in the sum of the component scores and can be any score from zero to 21. A high score means sleep quality is bad. Five was originally seen as the cutoff score. Participants that score below five have a good sleep quality. However, there is a tendency to use 6 as a cutoff score (Hametner et al., 2012) to be more selective. The internal consistency for the American and Japanese version was found to be good. Cronbach's alpha for the total score was .77 (Doi et al., 2000). The validity of the PSQI in patients with primary insomnia was good, since a high correlation between PSQI scores and a sleep diary was obtained by Backhaus and colleagues (Backhaus, Junghanns, Broocks, Riemann, & Hohagen, 2002). Moreover, they found a significant correlation between the PSQI and polysomnografic measurements. These results were confirmed in research on the Chinese version of the PSQI (Tsai et al., 2005). In all, the PSQI has a high sensitivity and specificity for patients with

insomnia (Backhaus et al., 2002) and also for patients with depression and schizophrenia (Doi et al., 2000).

2.3. Experiment

2.3.1. Needles. The needles (AcuPro C, Wujiang City Cloud & Dragon Medical Device Co., Ltd., China) that were used were 0.25 x 25 mm or 0.20 x 15 mm stainless steel (depending on the place of needling) single use needles. The needles were placed according to TCM principles.

2.3.2. Intervention. The participants in the acupuncture groups were given acupuncture treatment once a week, twelve weeks in a row. Individualized acupuncture according to TCM principles was applied after careful individual diagnosis by a licensed oriental medical practitioner with more than five years of clinical experience (MacPherson et al., 2010). Acupuncture treatment took place in a light room with (very) soft background music (Enya) playing. According to the demand of the ethics committee to decrease anxiety (Yu, Liu, Li, & Ma, 2009) as much as possible in patients with schizophrenia and to make them feel comfortable, music along with acupuncture was used. The music was kept constant over all participants and all sessions. There were 12 “relax” chairs in which it was possible to adjust the back and put the feet up, resulting in a near-lying position. It was, however, also possible to remain upright, this was left to the patients to decide for themselves. Due to the fact that acupuncture was applied with patients in a sitting or near lying position, access to acupuncture points on the back was limited. Patients came into the room in intervals, in order to reduce waiting time. Treatment (after needles were inserted) lasted for one hour. After this hour, needles were removed. This group treatment setting made sure practitioners were directly at hand in case anxiety would arise and it was one of the important points that were made in the dialogue with the ethics committee. In case individuals had personal questions or sensitive matters that needed to be discussed prior to treatment, there was an empty room next to the treatment room where confidentiality could be assured. As there were two acupuncturists present, the other patients would not be left alone in the mean time.
All participants continued with regular treatment including appointments with their psychiatrists, this was not influenced by the project since acupuncture was used as an add-on treatment.

2.3.3. Procedure. All participants were tested in an experimental testing room in the clinic, by apprentices who were blind to group or time of testing. The healthy control group was tested at T1 (pre-test) only, the participants with schizophrenia and depression were tested at T1 and T2 (post-test). After the tests at T1, participants were randomly divided into a treatment and a waiting list condition. The duration of the whole experiment was 13 weeks, which included 12 weekly acupuncture sessions and pre- and post-testing. At the end of the experiment, all participants received a debriefing and were individually informed about their

own test results. Patients on the waiting list were given the opportunity to attend acupuncture treatment after T2 if they wanted to. The current study stopped at T2, although acupuncture treatment was given after T2 in order to provide equal treatment opportunities. The patients, however, were not tested afterwards and therefore these data were not included in the study. Moreover, any acupuncture that was provided after the study was part of their normal treatment, not of any study.

2.4. Statistics. Differences between the five groups on the subtests of the PSQI before the start of the treatment were analyzed with a one-way analysis of variance (one-way ANOVA) with groups as between subjects factor, followed by post-hoc (Bonferroni) tests. Repeated measures analyses of variance were used to analyze possible differences on the PSQI Total Score and on the subtests of the PSQI pre- and post-treatment (in the four experimental groups), followed by post-hoc (Bonferroni) *t*-tests if appropriate, that is t(7) in our pilot-study. A value of $p < 0.05$ was considered to be statistically significant.

3. Results

3.1. Acupuncture Points that were used

Table 3.

Acupuncture points that were used.

Points/Patients	D1	D2	D3	D4	D5	D6	D7	D8	S1	S2	S3	S4	S5	S6	S7	S8
EX-HN-1	12	12	12	12	12	12	11	12	12	11	12	12	11	12	12	12
DU-24									2	5	5	2				8
DU-14										1						
DU-17									1							
DU-18									1							1
DU-19									1							
EX-HN-3	5		1			2										
EX-HN-5	5		1			2									1	
LI-20						1										
ST-8	10	3	3	9	8		7	2		7	5		10	1	2	1
ST-7									1							
ST-6					2											
TB-21							1						1			
KI-23						2										
KI-24					1	2			1							
KI-25					1				1							

(Table continues)

Points/Patients	D1	D2	D3	D4	D5	D6	D7	D8	S1	S2	S3	S4	S5	S6	S7	S8
KI-26									1							
GB-6	1															
GB-7									1							
GB-8									1	1						
GB-13									2	1	2		1			9
GB-20	2				1											
SI-3	5		11							2	2		1			
SI-4												1				
SI-5															2	
HT-2					1											
HT-3	1	4	3		3	1	4	2								
LI-4	12	12	12	12	12	12	12	12	7	3	5	9	10	8	12	4
PC-6	3	2		1	4	2			1	1		2	1	1	1	
PC-7		1			4			2	5	4	2	1	2		1	7
HT-7	12	12	11	12	12	12	12	12	9	1	7	3	3	8	3	
HT-8					1											

(Table continues)

Points/Patients	D1	D2	D3	D4	D5	D6	D7	D8	S1	S2	S3	S4	S5	S6	S7	S8
LU-5												1			1	
LU-6													8			
LU-7	1	11	8		5	3	3	12	8		1		3	5	1	
TB-5	5		10	3			2						2			
TB-6												1				
LI-7	1	2	1			2	10		2	1		1	1			
LI-11	6	6	3	12	10	1	12	6	5	10	8	8	8	11	12	11
CV-12																2
CV-14									1							
CV-15								1								
CV-16					1								1			
CV-17	7	2	3	7	10	1	7	9		12	3	6	9	9	8	11
CV-18					2									3	1	
ST-21										3						4
ST-25	4								2	1		3	5		1	3
CV-5											1					

(Table continues)

Points/Patients	D1	D2	D3	D4	D5	D6	D7	D8	S1	S2	S3	S4	S5	S6	S7	S8
CV-4	3	8	9		2			9								
KI-10			1	2												
SP-10	7	6	9			2	3	1				1				
BL-39													1			
BL-40													1	3		
SP-9	12	12	12	12	11	12	12	12	7	6	10	9	12	12	12	3
GB-34	8	7	5	7	8	6	5	6	1			1				4
ST-36	12	12	12	8	12	12	2	12	7	1	3	8	9	8	9	2
ST-40	1	1		12			11		1	10	9	3	2	4	2	9
SP-6	12	12	12	12	12	12	12	11	11	4	12	8	12	11	12	10
KI-3	11	12	12	12	12	12	12	12	1	2	4	7	11		12	
KI-5														2		
KI-6	9	8	9			5	8	12	2							2
LR-3	10	12	11	12	10	4	7	10	10	9	6	8	10	9	5	7
LR-1	2			2	4											
SP-4	4	4	1	11	4	7	9	7	1			2				

(Table continues)

Points/Patients	D1	D2	D3	D4	D5	D6	D7	D8	S1	S2	S3	S4	S5	S6	S7	S8
BL-60			2					2					1	3		
BL-62													2			
ST-44									2	7			1	3		7
ST-45				6			2				1			1		
GB-41												1				1
GB-44	3			9	6		2		1	5				4		2
GB-45														1		
BL-67	1	1			6	5		3	2		1	1	11	1		
Eye of the Knee						8		3		5				6		
BAXIE						3										

Note. D = Patient with depression, S = Patient with schizophrenia.

3.2.Pre-Test Results. Descriptive characteristics of the five different groups are shown in Table 4, as well as the outcomes of the post-hoc tests following the one-way ANOVA. On some of the subtests differences were found between the healthy control and the psychiatric groups.

Table 4.

Corrected means and SDs of the PSQI subtest scores at baseline (T1) for all groups.

PSQI Subtest	Schizophrenia Waiting list (*SD*)	Schizophrenia Acupuncture (*SD)*	Depression Waiting list (*SD*)	Depression Acupuncture (*SD*)	Healthy (*SD*)
Total Score	5.75 (1.91)	8.50 [b] (4.21)	9.63 [b] (4.57)	8.50 [b] (3.02)	3.50 (2.07)
Subjective Sleepquality	1.00 (.76)	1.00 (.76)	1.63 (.52)	1.38 (.52)	.75 (.46)
Latency	.87 (1.36)	1.88 (1.13)	1.50 (1.07)	1.50 (.93)	.50 (.54)
Duration	.25 (.46)	.38 (1.06)	1.00 (1.41)	.50 (.93)	.63 (.74)
Efficiency	1.38 (1.51)	1.00 (1.07)	1.13 (1.55)	1.00 (1.31)	.25 (.71)
Disorders	.88 (.35)	1.38 (.52)	1.63 (.74)	1.50 (.54)	.88 (.35)
Medication	.00 [a] (.00)	1.88 [b] (1.55)	1.25 (1.49)	.75 (1.39)	.00 (.00)
Daytime Sleepiness	1.38 (.52)	1.00 [b] (.76)	1.50 (.93)	1.88 (.84)	.50 (.54)

According to the one-way ANOVA (groups as between subjects factor) and post-hoc tests at baseline: [a] Mean is significantly different ($p < 0.05$) from the schizophrenia acupuncture group. [b] Mean is significantly different ($p < 0.05$) from the healthy control group.

3.3. Evaluation of Sleep Quality between the Groups

Table 5.

Corrected pre-test (T1) means of the PSQI for all five groups and post-test (T2) means of the PSQI for the four groups with patients.

	Schizophrenia Waiting list			Schizophrenia Acupuncture			Depression Waiting list			Depression Acupuncture			Healthy Control
PSQI Subtest	T1	T2	*P*	T1	T2	*P*	T1	T2	*P*	T1	T2	*P*	T1
Total Score	5.75	4.88	.576	8.50	5.50	.048*	9.63	9.00	.493	8.50	6.88	.003**	3.50
Subjective Quality	1.00	.75	.170	1.00	.50	.170	1.63	1.50	.685	1.38	1.00	.080	.75
Latency	.87	.75	.732	1.88	.75	.038*	1.50	1.63	.685	1.50	1.12	.197	.50
Duration	.25	.13	.598	.38	.63	.351	1.00	.75	.451	.50	.63	.351	.63
Efficiency	1.38	.63	.365	1.00	1.50	.407	1.13	1.38	.563	1.00	.75	.170	.25
Disorders	.88	.88	1.00	1.38	.88	.033*	1.63	1.63	1.00	1.50	1.13	.080	.88
Medication	.00	.38	.351	1.88	.38	.033*	1.25	.13	.094	.75	.75	1.00	.00
Daytime Sleepiness	1.38	1.38	1.00	1.00	.88	.685	1.50	2.00	.104	1.88	1.50	.080	.50

Note. Difference T1-T2 within the groups: *$p < 0.05$, **$p < 0.005$.

All patients randomized and treated over 12 weeks in the depression and schizophrenia group were analyzed (each $N = 8$).

As can be seen in Table 5, post hoc *t*-tests for each subtest and group separately resulted in the following significant differences: The depression acupuncture group showed a significant reduction for PSQI Total Score $t(7) = 4.333$, $p = 0.003$. For the depression waiting list condition, no significant differences were found between the pre- and post-test measurements. A significant reduction for the schizophrenia acupuncture group was found for PSQI Total Score $t(7) = 2.393$, $p = 0.048$, for PSQI Latency $t(7) = 2.553$, $p = 0.038$, for PSQI

Disorders $t(7) = 2.646$, $p = 0.033$, and for PSQI Medicine $t(7) = 2.646$, $p = 0.033$. No differences were found for the schizophrenia waiting list condition.

3.4. Side Effects. Two patients reported bruising as a side effect after one of the acupuncture treatment sessions. Moreover, one patient reported having been extremely tired after the first session. Otherwise, no side effects were reported.

4. Discussion

In this pilot study, the effects of three months of acupuncture treatment on subjective sleep quality were investigated in a group of patients with schizophrenia and a group of patients with depression that were diagnosed by their therapists according to the ICD-10 (World Health Organization, 1992). All patients were chronically ill. Significant improvements were found on the PSQI Total Score for both treatment groups, indicating that patients slept better after 12 acupuncture treatments. The waiting list condition groups showed no significant improvements. As was suggested by Hametner and colleagues (Hametner et al., 2012), a cutoff score of six can be used in order to clinically divide patients with sleep problems from patients with good sleep. The patient group with schizophrenia falls below this clinically relevant score after treatment. The patient group with depression has improved and although the differences might not seem large, they seem borderline clinically relevant.

Three subscales (PSQI Latency, PSQI Medication, and PSQI Disorders) showed significant improvements in the schizophrenia group, but not in the depression group. This indicates that the patients with schizophrenia took more benefit from acupuncture than the patients with depression. Of note, these patients fell asleep faster and even approached normal levels on the subtest (PSQI Latency), meaning that patients with schizophrenia lay awake less long before falling asleep after acupuncture treatment and that they reached levels that are commonly found in healthy controls. They also used less medication in order to sleep and reached normative levels also on the subtest for sleep disorders. Five of the patients with schizophrenia (from the acupuncture condition) used sleep medication of different kinds beforehand, whereas four of them answered that they had stopped using this medication during the time of the acupuncture treatment. Moreover, one of the patients in the waiting list condition of this group, who had not used sleep medication beforehand, started using sleep medication. On the other hand, six of the patients with depression (two in the acupuncture group and four in the waiting list condition) used sleep medication beforehand of which four (in the waiting list condition) stopped using this medication and one of the other patients in the waiting list group started to use sleep medication. There were no differences between or within the depression groups on medication use as reported by the patient.

The intervention phase lasted three months (12 treatments) only. Future studies might consider whether the novelty factor of this intervention or the short term availability implies

that patients are more likely to attend. It is not known whether patients would be so keen to attend acupuncture were it available as part of their normal treatment package. There were no withdrawals from the acupuncture or waiting list groups in this study. In this clinic, as part of the normal treatment package, patients can choose to visit treatment groups like for instance: a psychosis education group, sleep training, depression group, social competency training group or a memory training. All of these groups last 10 to 12 times and have a dropout rate between 30 to 40%. These differences between the regular groups and this study might be caused by the small amount of appointments in the waiting list condition as well as a positive experience in the acupuncture groups. This impression is supported by the absent dropout and the comments made by participants (that reported for instance: feeling less tired, more relaxed and better able to sleep), that they were satisfied with the treatment and keen to have it. On the other hand, it is important to note that the participants were largely self-selecting (as they are in every group they attend in this clinic) and therefore more likely to come to the treatments anyway. However, in order to draw more firm conclusions, it would have been better to implement a measure of treatment satisfaction in the study.

Some participants reduced their medication, in consultation with their psychiatrist, as a result of the acupuncture treatment. These participants saw this as a benefit of the acupuncture. Medication reduction is usually seen as positive by patients. It is felt to be a sense of improvement or achievement. It may be that the promise of a reduction in medication through acupuncture may be a motivational factor for attendance at acupuncture treatments. On the other hand, it is important to note that there are possible pitfalls in reducing medication as well. It has been described that patients with schizophrenia who improve through the use of acupuncture and as a result reduce or even stop taking medication may become more vulnerable to breakdown (Ronan, Robinson, Harbinson, & MacInnes, 2011). Further research is needed to confirm these subjective comments that were reported by the patients in this study and to investigate the possibility that acupuncture may be misused as an excuse for non-adherence with conventional medication.

Limitations: Since the study involves acupuncture, it is obvious that the problem of the absence of a suitable control group or placebo needs to be mentioned (MacPherson et al., 2010). In this study, it was chosen to investigate the “normal” or “real world” manual individualized acupuncture treatment that any patient would receive if they should go to an oriental medical practitioner. The use of a standardized protocol for acupuncture is, besides the National Acupuncture Detoxification Association (NADA) protocol that is used for addiction and trauma (Cui, Wu, & Luo, 2008), unheard of in clinical TCM practice. The use of such a standardization would therefore not shed any light on the possible effect that an acupuncture add-on treatment (that patients seek outside our psychiatric clinics) would have on patients and would not be generalisable to routine clinical practice (Schroer & Adamson, 2011). In this study, a pragmatic randomized controlled trial (RCT) was used; this approach attempts to answer a “real world” question whether acupuncture as add-on treatment improves sleep more than without this treatment. Our overall goal was to deliver

better treatment to patients and this implies that we have to evaluate what can be done in daily practice. MacPherson (MacPherson, 2000) paraphrased this issue by stating that “the question in acupuncture research should be rather whether acupuncture is of better value than what is currently on offer instead of asking whether acupuncture is better than placebo?”

Due to the ethical problems related to discontinuing treatment with antipsychotic and antidepressant drugs, patients continued their medication during the study. We have listed the doses in Chlorpromazine equivalents and information on medication that was used in Table 2. Due to the fact that psychiatric patients use a wide variety of medication, it was not possible, within the convenient sample in our mono-center pilot study, to include only those that use the same medication and medication doses.

One more limitation of the study is the fact that a second baseline might have been used, it is recommended for future research.

Since the ethics committee required group treatments due to the fact that a practitioner needed to be present at all times, a limitation was that some participants talked to each other before, during or after treatment sessions. It was not possible to control for the content of these conversations.

Finally, the number of patients in the present study is relatively small. Therefore, in further research it is necessary to increase the sample size, though, despite the small numbers, significant improvements in sleep quality were found.

There is anxiety about giving acupuncture to people with schizophrenia in Europe, since it is not normally practiced and people in psychiatric hospitals are not normally left alone with needles or other dangerous objects. Moreover, anxiety exists about the needles becoming part of hallucinations or psychotic thoughts. For instance, patients might think that they are being radiographic controlled through the needles. The present study further proves that people with schizophrenia can be safely treated with acupuncture and that the use of needles did not evoke negative emotional reactions.

It is important to realize that in this pilot study, positive results were obtained in a group of patients with schizophrenia that have been ill for more than 10 years. Length of illness was analyzed more specifically and it was found that, although there was a difference between the schizophrenia and depression experimental and waiting list groups when it comes to this factor, it did not account for the more significant results in the group with schizophrenia.

It is obvious that the positive outcomes of this pilot study warrant further and larger scale research, but the tentative conclusion is that the present study shows that acupuncture seems to influence sleep in a positive way in sleep disturbed patients and seems a suitable add-on treatment in psychiatry, even in patients with long-term depression or schizophrenia.

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Chapter 5

Sleep disorders in patients with depression or schizophrenia: A randomized controlled trial using acupuncture treatment

Based on:

Bosch, P., Van den Noort, M., Staudte, H., Lim, S., Yeo, S., Coenen, A., & van Luijtelaar, G., (under review/2015c). Sleep disorders in patients with depression or schizophrenia: A randomized controlled trial using acupuncture treatment. *Explore: The Journal of Science and Healing*.

Abstract

Objective: The purpose of this preliminary clinical trial was to investigate whether acupuncture has a positive influence on sleep and symptomatology in patients with schizophrenia or depression.
Design: A randomized controlled trial.
Patients and Methods: One hundred participants were recruited: 40 outpatients with schizophrenia, 40 outpatients with depression, and 20 healthy controls. They all filled in a depression inventory, and the positive and negative symptoms of the patients with schizophrenia were evaluated by their psychiatrists. All participants were asked to complete a sleep log for two weeks. For the psychiatric patients, a randomized design with experimental (three months of acupuncture treatment) and control (waitlist) conditions was used, after which all measurements were conducted once more.
Results: Before treatment, patients with depression were awake longer during the night, needed more time to fall asleep, evaluated their sleep as less relaxed, felt more exhausted, and reported a lower average performance level than healthy controls did. Moreover, patients with depression slept shorter and felt more exhausted than patients with schizophrenia. Patients with schizophrenia solely reported a lower average performance level compared to healthy controls. Acupuncture slightly improved sleep and depressive symptoms in patients with depression, but did not affect sleep nor influence positive and negative symptoms in patients with schizophrenia.
Conclusions: These preliminary data suggest that acupuncture can be used in order to reduce symptoms and improve sleep to some extent in patients with depression, but does not seem to have beneficial effects for patients with schizophrenia.

INTRODUCTION

Epidemiological studies show that approximately 40 million people in the USA suffer from sleep disorders (Luppi, 2005) and that 20% to 35% of the population show symptoms that are related to insomnia (Ford & Kamerow, 1989; Leger, Guilleminault, Dreyfus, Delahaye, & Paillard, 2000; Ohayon, Caulet, & Lemoine, 1998); moreover, 57% of the patients with insomnia have a psychiatric disorder or develop one in the next year (Ford & Kamerow, 1989). Insomnia and nightmares are important predictors of depressive symptoms (Buysse et al., 2008; Cukrowicz et al., 2006), and depressive symptoms are risk factors for insomnia (Katz & McHorney, 1998); therefore, the relation between depression and sleep disorders seems to be bidirectional (Morawetz, 2003; Roberts, Shema, Kaplan, & Strawbridge, 2000; Taylor, Lichstein, Durrence, Reidel, & Bush, 2005).

Sleep disorders are found in about 30 - 80% of the patients with schizophrenia (Cohrs, 2008) and in more than 80% of the patients with depression (Reynolds & Kupfer, 1987). Moreover, problems with sleep are among the complaints that occur most often before a patient has a recurrent episode (Herz, 1985; Kerkhofs, 1997; Monti & Monti, 2004; Perlis et al., 1997; Reynolds et al., 1997). In their longitudinal study, Sands and Harrow (1999) found that about one-third of the patients with schizophrenia suffered from depression, and a depression that was neither recognized nor treated could cause sleep disorders (Costa e Silva, 2006).

Compared to healthy controls, patients with schizophrenia were found to have a larger sleep latency in combination with a decreased total sleep time, decreased sleep efficiency, less time in phase-3 and -4 sleep (deep sleep), and longer REM sleep latency (Chouinard, Poulin, Stip, & Godbout, 2004). Indications exist that in patients with schizophrenia, decreased sleep efficiency may be caused by longer sleep latency and an increased number of awakenings during the night (Benson, Faull, & Zarcone, 1991).

Sleep disorders, especially in vulnerable patients with depression as well as those with schizophrenia, should be treated due to the beneficial overall influence of good sleep (Benson, 2006). This is not only relevant for these patients, but also for society, because an improvement in sleep is estimated to lead to lower costs; yearly costs for insomnia for the USA alone are estimated to be $30 to $35 billion (Walsh & Engelhardt, 1999).

Different methods exist for the treatment of sleep disorders (Pagel & Parnes, 2001). Traditionally, pharmacological interventions are used (Montgomery & Dennis, 2003). Previously, benzodiazepines were prescribed for the treatment of sleep disorders, but nowadays, non-benzodiazepine hypnotic medications, like zolpidem, zaleplon, and eszopiclone, are often prescribed because they have a lower risk of tolerance and abuse (Richey & Krystal, 2011). Also, psychological treatments, like stimulus control therapy, relaxation, paradoxical intention, sleep restriction, and cognitive-behavior therapy are frequently used (Morin et al., 2006). One relatively new method in non-Asian countries for the treatment of sleep disorders is the use of acupuncture as a non-pharmacological

intervention technique because evidence exists that it may have beneficial effects as a treatment for insomnia (Cao, Pan, Li, & Liu, 2009; Reshef et al., 2013; Zhao, 2013).

The aim of this study was to investigate whether acupuncture has a positive influence on sleep in patients with schizophrenia and patients with depression. Before treatment (at baseline), we expected that patients with depression and patients with schizophrenia would sleep worse than the healthy controls and that, in line with the literature, the patients with depression would have the worst sleep of the three groups. Our hypothesis was that acupuncture would have a beneficial effect on sleep in patients with depression and in patients with schizophrenia and that typical symptoms would decrease.

METHODS

Design overview

In this study, an experimental (three months of acupuncture treatment) and a control (on a waitlist for over three months) condition were used. All participants were asked to complete a sleep log for two weeks in order to establish a baseline (T1) measurement. The healthy control group was not treated with acupuncture; while no clinical effect of acupuncture could be expected in healthy participants (previous research has shown that acupuncture has a modulating and normalizing effect) (Bosch, Staudte, van den Noort, & Lim, 2014; Hui, Marina, Liu, Rosen, & Kwong, 2010), they were only included to establish reference values in the current cultural and geographical cohort and were only used in the tests at T1. In the patient groups, two measurements were taken: before (T1) and after acupuncture treatment or a waitlist period (T2). Note that the sleep log had to be filled in every morning and evening just after waking up and before going to sleep (Fischer, Mayer, Peter, Riemann, & Sitter, 2002), which took approximately 10 minutes a day. Previous research showed that the sleep log was a reliable instrument for registering sleep in patients; in a study by Rogers, Caruso, and Aldrich (1993), for instance, subjective data taken from sleep logs was found to be comparable to data from polysomnography (kappa = 0.87). Moreover, the sensitivity and the specificity of the sleep logs in this study (Rogers et al., 1993) were found to be 92.3% and 95.6%, respectively. In addition to the sleep log, both the patients with depression and the patients with schizophrenia filled in a typical clinical instrument, namely, the Becks Depression Inventory-II (BDI-II) (Beck, Steer, & Brown, 1996), to assess depression before and after the treatment or the waitlist period. The severity of the schizophrenia symptoms was assessed using the Positive and Negative Symptom Scale (PANSS) (Kay, Fiszbein, & Opler, 1987), which was filled in by each patient's psychiatrist before and after the treatment or the waitlist period of three months. The current study was approved by the local ethics committee (Ärztekammer Nordrhein, trial number: 2008331).

Setting and participants

In total, 100 participants were enrolled in this study: 40 patients with schizophrenia, 40 patients with depression, and 20 healthy controls. Participants were recruited at the LVR-

Klinik Bedburg-Hau. All patients were outpatients who had received regular care at a psychiatric department. There were 22 female and 18 male adult patients with schizophrenia (average age = 42.20, standard deviation (*SD*) = 10.11 years), there were 33 female and 7 male adult patients with depression (average age = 48.37, *SD* = 8.88 years), and there were 11 female and 9 male adult healthy controls (average age = 33.05, *SD* = 11.27 years). The inclusion criterion for all participants was that they be between 18 and 65 years of age. The exclusion criteria for the patients with depression and the patients with schizophrenia were epilepsy, substance abuse, and other neurological disorders. For the healthy control participants, the exclusion criteria were the presence of any neurological or psychiatric disorder or substance abuse. All participants of our study took part voluntarily without any inducement.

Randomization and intervention

Participants were randomly divided into an experimental or a control group. In the experimental group, acupuncture treatment was given as intervention to the participant once a week. In total twelve treatments were given, each lasting one hour after needle insertion. In the control group, the participants were on a waitlist and only received their regular care; no extra interventions were offered.

Acupuncture as clinical intervention

Individualized acupuncture was used after careful individual diagnosis by a licensed Oriental medical practitioner with more than five years of clinical experience (MacPherson et al., 2010). The single-use needles (AcuPro C, Wujiang City Cloud & Dragon Medical Device Co., Ltd., China) for the acupuncture treatment were 0.25 x 25 mm or 0.20 x 15 mm stainless-steel needles, depending on the location on the body. For both the individualized acupuncture, as well as for the individual clinical diagnosis, the principles of Traditional Chinese Medicine (TCM) were followed (Bosch et al., 2013).

Outcome sleep logs

The primary outcome measures in this study were the scores on the following six sleep variables of the sleep log at T1: 1. "*Total sleep time*", 2. "*How many minutes awake during the night?*", 3. "*How many minutes awake before falling asleep*?" 4. "*How relaxing was your sleep?*", 5. "*Did you feel exhausted?*", and 6. "*How was your average performance level today?*" (Note that the first three sleep variables are the more "objective" ones and that the last three sleep variables are the more "subjective" ones.) The secondary outcome measures in our study were the difference scores (between "before" (T1) and "after treatment/waitlist" (T2)) for the same six sleep variables.

Outcome clinical tests

Further outcome measures were the scores on the BDI-II at baseline and the differences on the BDI-II between T1 and T2 within the groups. Moreover, the scores on the PANSS

subscales (PANSSPOS, measuring the positive symptoms, PANSSNEG, measuring the negative symptoms, PANSSPSYCHO measuring general psychopathology and PANSSTOT measuring the total score on the PANSS) at T1, as well as the differences between the scores at T1 and T2, within the groups were further outcome measures.

Data analyses

As a result of the large drop-out of participants, mostly lost during the waitlist period for the schizophrenia group, differences between the two psychiatric groups for the six sleep variables before (baseline = T1) and after acupuncture treatment (T2) were analyzed separately. Moreover, at T1 a healthy control group was included.

At T1, the scores for the six sleep variables of the sleep log were analyzed with a one-way analysis of variance (ANOVA) by using SPSS version 22.0 (IBM Corp., 2013) to indicate whether the three groups differed significantly across the different sleep variables. The dependent variables were the scores for the sleep variables and the between-subjects factor was the group (depression, schizophrenia, or healthy control group). A significance level of $P < .05$ was used.

The results on the sleep log data at T2 should have been analyzed together with their T1 counterparts by using General Linear Model (GLM) repeated measures or difference scores in order to compare the results of the two psychiatric groups for the six sleep variables before (T1) and after acupuncture treatment (T2). Due to the large drop-out, especially in the schizophrenia waitlist group, however, the scores for the sleep variables were analyzed with a one way ANOVA for three groups: depression treatment, depression waitlist, schizophrenia treatment groups.

The BDI-II data were more complete, and a sufficient number of participants were present at T1 and T2 for meaningful statistical analyses (although the number of subjects with schizophrenia on the waitlist was only seven). First, data at T1 were analyzed with an ANOVA with groups (depression waitlist, depression treatment, schizophrenia waitlist, schizophrenia treatment) as between-subjects factor, followed by post-hoc tests. Next differences between T1 and T2 were established for all groups by using paired sampled Student t-tests. The PANSS data were only collected for the patients with schizophrenia, and the differences between T1 and T2 were analyzed by using GLM repeated measures. Only significant group differences are reported.

RESULTS

Sleep log results at baseline

Table 1.

Overview of the Sleep Log Results at Baseline (T1) for the Depression Group, the Schizophrenia Group, and the Control Group

Sleep variable	Depression (N^1 = 28)	Schizophrenia (N = 20)	Control (N = 18)
How long have you slept?[2]	7.17 (0.83)[a]	7.98 (1.25)	7.43 (0.64)
How long (min.) were you awake during the night?	20.52 (21.05)[b]	11.88 (9.35)	3.16 (3.64)
How long did it take before falling asleep?[3]	30.29 (19.70)[b])	26.17 (25.19)	14.31 (11.30)
How relaxing was your sleep?[4]	3.28 (1.84)[a,b]	2.37 (0.72)	2.23 (0.55)
Have you felt exhausted?[5]	1.39 (0.56)[a,b]	0.92 (0.75)	0.77 (0.44)
How was your average achievement today?[6]	3.15 (0.55)[a,b]	2.67 (0.88)[b]	2.08 (0.56)

Note. [1] *N* = number of participants.

[2] In hours.

[3] In minutes.

[4] On a 5 point scale (1 = very relaxing; 5 = not at all relaxing).

[5] On a 4 point scale (0 = no; 3 = very).

[6] On a 6 point scale (1 = good; 6 = bad).

[a] Average score is significantly different ($p < .05$) from the average score for the group with schizophrenia.

[b] Average score is significantly different ($p < .05$) from the average score for the control group.

As can be seen in Table 1, the ANOVA showed a significant group effect ($F_{(2,59)} = 4.03$, $p < .05$, $eta^2 = .120$) on the "*Total sleep time*": patients with depression slept less than patients with schizophrenia ($p < .01$). The analyses of the "*How many minutes awake during the night?*" ($F_{(2,58)} = 7.54$, $p = .001$, $eta^2 = .206$) and of "*How many minutes awake before falling sleep?*" ($F_{(2,59)} = 3.48$, $p < .05$, $eta^2 = .105$) showed a group effect. In both cases, the patients with depression were awake longer than the healthy controls (*p's* < .05). The more subjective sleep results (see also Table 1), where the participants had to indicate how they evaluated their sleep, also showed differences between the three groups. Significant group effects ($F_{(2,62)} = 4.59$, $p < .05$, $eta^2 = .129$) were found for "*How relaxing was your sleep?*" and "*Did you feel exhausted?*" ($F_{(2,62)} = 6.60$, $p < .01$, $eta^2 = .175$) and for "*How was your average performance level today?*" ($F_{(2,63)} = 14.05$, $p < .000$, $eta^2 = .308$). The patients with depression evaluated their sleep as less relaxing and were more exhausted compared to the patients with schizophrenia and the healthy control participants (*p's* < .05). Both patient groups indicated their average performance level as worse (*p*'s < .01) compared to the healthy control participants. Moreover, the patients with depression evaluated their average performance level as being worse than that of the patients with schizophrenia ($p < .01$).

Clinical tests at baseline

Table 2.

Overview of the BDI-II at Baseline (T1) and after Treatment or after Waitlist (T2) for the Depression Waitlist Group, the Depression Treatment Group, the Schizophrenia Waitlist Group and the Schizophrenia Treatment Group. Overview of the PANSS POS, PANSS NEG, PANSS PSYCHO, and the PANSS TOT scores at Baseline (T1) and after Treatment or after Waitlist (T2) for the Schizophrenia Waitlist and the Schizophrenia Treatment Groups.

Variable	**Depression Group**				**Schizophrenia Group**			
	WL[1] T1	**WL[1] T2**	**TR[2] T1**	**TR[2] T2**	**WL[1] T1**	**WL[1] T2**	**TR[2] T1**	**TR[2] T2**
BDI-II	24.83 *(12.12)*[c,3] (*N*[4] = 18)	22.19 *(11.46)*[c] (*N* = 16)	24.72 *(10.77)*[c] (*N* = 18)	15.53 *(10.97)* (*N* = 15)	14.00 *(10.52)* (*N* = 19)	10.29 *(11.76)* (*N* = 7)	13.25 *(10.43)* (*N* = 20)	12.81 *(7.65)* (*N* = 16)
PANSS POS	NA	NA	NA	NA	15.07 *(7.55)* (*N* = 14)	13.38 *(6.46)* (*N* = 8)	12.56 *(4.77)* (*N* = 18)	12.35 *(4.83)* (*N* = 17)
PANSS NEG	NA	NA	NA	NA	17.14 *(5.59)* (*N* = 14)	17.38 *(4.66)* (*N* = 8)	21.50 *(10.96)* (*N* = 18)	20.00 (*10.34)* (*N* = 17)
PANSS PSYCHO	NA	NA	NA	NA	39.64 *(12.20)* (*N* = 14)	37.50 *(10.66)* (*N* = 8)	40.50 (*14.65*) (*N* = 18)	37.47 *(12.23)* (*N* = 17)
PANSS TOT	NA	NA	NA	NA	71.93 *(19.52)* (*N* = 14)	68.50 *(18.74)* (*N* = 8)	74.56 *(27.65)* (*N* = 18)	69.82 *(25.30)* (*N* = 17)

Note. [a] Significantly different from the depression treatment group.

[b] Significantly different from the schizophrenia treatment group.

[c] Significantly different from the total schizophrenia group.

[1] WL = waitlist condition.

[2] TR = treatment condition.

[3] Standard deviation.

[4] *N* = number of participants.

NA = not applicable.

The ANOVA of the BDI-II scores showed a significant group effect ($F_{(3,73)} = 5.82$, $p < .001$, $eta^2 = .19$), and post-hoc tests showed that the two groups with depression obviously scored higher than the two schizophrenia subgroups. The PANSS scores were only measured for the patients with schizophrenia and were not different between the treatment and the waitlist subgroups. All BDI-II and PANSS scores at T1 and T2 can be found in Table 2.

Sleep log acupuncture effects

Table 3.

Overview of the Sleep Log Results After Acupuncture Treatment versus After Waitlist for the Depression Treatment Group (N = 10), the Depression Waitlist Group (N = 8) and the Schizophrenia Treatment Group (N = 6)

	After Acupuncture		**After Waitlist**
Sleep variable	*Depression (N[1] = 10)*	*Schizophrenia (N = 6)*	*Depression (N = 8)*
Total sleep time?[2]	7.11 (0.72)	7.90 (0.90)	7.28 (1.52)
How many minutes awake during the night?	11.65 (10.60)	3.36 (4.68)	33.63 (72.96)
How many minutes awake before falling asleep?[3]	24.93 (16.38)	13.59 (7.41)	34.69 (19.58)
How relaxing was your sleep?[4]	2.47 (0.17)[a]	2.37 (0.22) [a]	3.08 (0.19)
Did you feel exhausted?[5]	1.19 (0.48)	0.72 (0.70)	1.57 (0.55)
How was your average performance level today?[6]	3.135 (0.82)	2.99 (.9.14)	3.29 (0.68)

Note. [1] N = number of participants.

[2] In hours.

[3] In minutes.

[4] On a 5 point scale (1 = very relaxing; 5 = not at all).

[5] On a 4 point scale (0 = not; 3 = very).

[6] On a 6 point scale (1 = good; 6 = bad).

[a] Mean score is significantly different ($p < .05$) from the mean score for the Depression Waitlist group.

[b] Mean score is significantly different ($p < .05$) from the mean score for the schizophrenia group after acupuncture treatment.

The schizophrenia waitlist group was no longer motivated to fill out the sleep log after the waitlist period: most patients reported that it was too much of an effort to think of the sleep log twice a day for two weeks. In this group, only three persons returned the form; therefore,

this group was not included in the statistics at T2. As can be seen in Table 2, the ANOVAs on the six sleep variables ("After acupuncture" – "After waitlist") for the remaining three groups (schizophrenia treatment group, depression treatment group and depression waitlist group) revealed a significant treatment effect on *"How relaxing was your sleep?"* ($F_{(2,21)}$ = 3.951, p < .05, eta^2 = .273) and on *"Did you feel exhausted?"* ($F_{(2,21)}$ = 1,256, p < .05, eta^2 = .274). Post-hoc analyses revealed that both acupuncture groups evaluated their sleep as more (*p's* < .05) relaxed than the waitlist group and that the group with schizophrenia was less exhausted than the waitlist group (p < .05). On the variable "*How many minutes awake before falling asleep?*", a trend (p = .07) was found ($F_{(2,20)}$ = 2.996, p = .07, eta^2 = .231): the schizophrenia acupuncture group tended to be awake for less time than the waitlist group. Differences within the groups between T1 and T2 were analyzed, but no significant differences were found, partly due to large data loss related to the dropout.

Acupuncture effects on the clinical tests

The paired samples *t*-tests showed a significant lower BDI-II score on T2 (compared to T1) for the depression treatment group (t (14) = 3.48, p < .01) only. Neither the PANSS subscales nor the PANSS total score showed any within-group or between-group effects.

DISCUSSION

The aim of this study was to investigate whether acupuncture has a positive influence on sleep in patients with schizophrenia or depression. The hypotheses were that at baseline, patients with depression or schizophrenia would sleep less than the healthy controls and that the patients with depression would have the worst sleep of the three groups. Moreover, we expected that acupuncture would have a beneficial effect both on sleep and depressive symptoms in patients with depression or schizophrenia and on the positive and the negative symptoms in patients with schizophrenia.

At baseline, the sleep log results of the present study (see also Table 1) showed that, as was expected based on previous reports (Cohrs, 2008; Reynolds & Kupfer, 1987; Tsuno, Besset, & Ritchie, 2005), the patients with depression reported more sleep problems than the patients with schizophrenia and the healthy control participants. This pattern was visible in both the more objective sleep measures, the shorter length of sleep, the longer period of lying awake longer during the night and the longer sleep latency, and the more subjective sleep measures on which participants with depression evaluated their sleep, i.e., being less relaxed, feeling more tired, and functioning less well during the day. Patients with depression slept just as long as the healthy controls, but showed worse results on all other variables. In addition, they felt more exhausted and slept shorter than the patients in the schizophrenia group.

In contrast to previous research (Hofstetter, Lysaker, & Mayeda, 2005; Lunsford-Avery et al., 2013; Royuela et al., 2002) and therefore against our hypothesis, the patients with schizophrenia evaluated their sleep as being rather similar to that of the healthy control

participants. The only exception was that they evaluated their average performance level of the day as worse than that of the healthy control group. The fact that patients with chronic schizophrenia score more in the normal range than one might expect is in line with a recent clinical study on personality and psychopathology in patients with long-term schizophrenia; that study also showed relatively few deviations from the healthy control group (Bosch et al., 2014).

With respect to the possible acupuncture effect on sleep, a second main finding of this study was that the depression and the schizophrenia treatment groups evaluated their sleep at T2 as being more relaxed than that of the waitlist group while the evaluations of the two treatment groups did not differ. Furthermore, the individuals with schizophrenia felt less exhausted than the patients with depression in the waitlist subgroup at T2. Acupuncture had a positive effect on these two subjective variables, confirming the findings by Spence and colleagues that acupuncture seems to have a relaxing effect on patients with psychiatric problems (Spence et al., 2004). In addition, for a more objective variable, a tendency towards acupuncture having a positive effect was found: The individuals with schizophrenia tended to lie awake for a shorter time than the waitlist group that had not received any additional treatment whereas the times lying awake for both depression groups were not different. No beneficial effects of acupuncture were found for the other two objective variables (the total sleep time and the number of minutes being awake during the night) or for the third subjective variable (the average performance level) (see Table 3). These results are partly in line with the results by Reshef and colleagues (Reshef et al., 2013; Zhao, 2013), who found no significant improvements on questionnaires that patients had to fill in, but did find improvements on actiwatch data for their patients with schizophrenia.

With respect to the clinical symptoms, at baseline, the groups with depression had the expected elevated BDI-II scores, often in the clinical range, and did not differ from each other. The groups with schizophrenia naturally scored as being less depressed and did not differ from each other at baseline (Beck et al., 1996). In general, the patients with depression scored in the range 20-28, indicating moderate depression, while the patients with schizophrenia scored in the range 14-19, indicating mild depression (Beck, Steer, Ball, & Ranieri, 1996). The PANSS (Kay et al., 1987) scores were only assessed for the patients with schizophrenia and were not different between the treatment and the waitlist subgroups (see also Table 2). In general, the PANSS scores showed that the patients were suffering from mildly to moderately severe positive and negative symptoms (the cut-off PANSS TOT score is 75 for moderate symptoms, with a lower score indicating symptoms that are less severe) (Leucht et al., 2005).

With respect to the possible acupuncture effect on clinical symptoms, the depression acupuncture group improved significantly more on the BDI-II (Beck et al., 1996) than the depression waitlist group at T2 and differed significantly from its own score at T1, indicating a positive effect of the acupuncture treatment. The schizophrenia groups did not differ from each other, and no differences within and between the schizophrenia treatment and waitlist groups were found on the PANSS (Kay et al., 1987) on T2.

In sum, acupuncture treatment was found to improve the depressive symptoms of the patients with depression but not the symptoms of the patients with schizophrenia. The depression treatment group moved from “moderate depression” to “mild depression”, and these clinically- relevant treatment effects were also visible on an individual level, showing that patients moved from one clinical cut-off score to another (for instance, from “moderate depression” to “mild depression”). Moreover, acupuncture did not have a beneficial effect on the positive and the negative symptoms in patients with schizophrenia (see Table 2). This might be explained by their relatively low scores at T1 (mildly to moderately severe, even below the cut-off PANSS TOT score of 75) (Leucht et al., 2005). The supposed normalizing effect of acupuncture would cause more differences in patients that show more severe scores than in those that show only mild scores.

Naturally, the present study has several limitations. In line with previous clinical acupuncture studies (Fogarty, Harris, Zaslawski, McAinch, & Stojanovska, 2010; Shin et al., 2013), as well as previous clinical studies on depression (Ibrahim et al., 2012) and schizophrenia (Egan et al., 2013), a design with an experimental (three months of acupuncture treatment) and a control (waitlist) group was chosen. Unfortunately, during our study, most participants in the waitlist subgroup of the schizophrenia group dropped out. Participants turned out not to be willing to wait for three months before filling out the same forms again, even though they would have been allowed to receive acupuncture treatment after the second test period. Of the 40 participants in the total waitlist group, 29 (73%) participants were lost for the sleep log data, the dropout rate being greater for the patients with schizophrenia (85%) than for the patients with depression (60%). Especially, the patients with schizophrenia felt that too much effort was required to fill in the sleep log every day. This is further supported by the fact that a much higher percentage (60% in total) of the patients with schizophrenia could be motivated to fill in the BDI-II (Beck et al., 1996), more than twice as many as those who could be motivated to fill in the sleep log (25%) (Fischer et al., 2002). It would have been better to have used a less time-consuming sleep questionnaire, such as the Pittsburgh Sleep Quality Inventory (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) or the Epworth Sleepiness Scale (Johns, 1991), or even better to have used actiwatches (Van de Wouw, Evenhuis, & Echteld, 2013) because actiwatches provide an opportunity to collect objective sleep quality data (van de Wouw et al., 2013) from patients with depression and patients with schizophrenia without requiring for a daily effort.

All patients continued their medication during the study. For ethical reasons (Fulford & Howse, 1993), stopping the treatment of psychiatric patients with antipsychotic and antidepressant drugs was not possible. In addition, because the participants in the present study used a wide variety of medications, better control of the type and the doses of the medications was impossible.

Finally, the sample sizes in the present psychiatric study are relatively small (Streiner, 1990). For practical reasons (Patel, Doku, & Tennakoon, 2003), the recruitment of more patients with schizophrenia and more patients with depression at our clinic was not possible,

which is a common problem in clinical acupuncture research (Pilkington, 2010). In future research, a multicenter study (Alcolea et al., 2014; López et al., 2004; Messerer, Porzsolt, Hasford, & Neiss, 1987; Reid, Hely, Morris, Loy, & Halliday, 2011) seems to be an interesting alternative not only to increase the sample size but also to exclude effects of practitioner bias and the experimental/clinical atmosphere (Messerer et al., 1987).

Conclusions

The present preliminary clinical data suggest that acupuncture seems to be a safe and useful non-pharmacological clinical intervention technique for improving sleep to some extent in patients with depression, but not in patients with schizophrenia. Acupuncture treatment was found to improve the depressive symptoms of the patients with depression, but not the symptoms of the patients with schizophrenia; moreover, it did not have a beneficial effect on the positive and the negative symptoms in the patients with schizophrenia. The question of whether the anti-depressive effects in the group with depression are caused by their improved quality of sleep or whether the improved quality of sleep is caused by the alleviation of the depressive symptoms cannot be answered with the present data because of the cause-and-effect problem resulting from the bidirectional associations between sleep and depression that has been reported in the literature (Franzen & Buysse, 2008). Further and more extensive research using more objective sleep measurements and more extensive scales for depression might be able to answer this question. All in all, these data justify further research into the possible use of acupuncture in the treatment of depression.

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Chapter 6

The effect of acupuncture on mood and working memory in patients with depression and schizophrenia

Based on:

Bosch, P., Van den Noort, M., Staudte, H., Yeo, S., Lim, S., Coenen, A., & van Luijtelaar, G., (in press/2015d). The effect of acupuncture on mood and working memory in patients with depression and schizophrenia. *Journal of Integrative Medicine*.

ABSTRACT

OBJECTIVE: This study investigates the mood and the working memory performance in patients with depression or schizophrenia and whether acupuncture can improve these.
METHODS: A pragmatic clinical trial design was used. The study was conducted in a psychiatric clinic. Fifty patients with depression and 50 with schizophrenia were randomly divided into an experimental and a waiting-list group. Additionally, 25 healthy control participants were included. Twelve weeks of individualized acupuncture treatment was used as clinical intervention. All patients were tested before (T1) and after acupuncture treatment (T2) on a mood scale (Becks Depression Inventory-II, BDI-II), a simple working memory task (digit span), and a complex working memory task (letter-number sequencing); the healthy controls were tested at T1 only.
RESULTS: Patients with depression scored worse than the others on the BDI-II, and patients with schizophrenia scored worse than the healthy controls. On the digit span, patients with schizophrenia did not differ from healthy controls whereas they scored worse of all on the letter-number sequencing. With respect to the acupuncture findings, first, the present study showed that the use of acupuncture to treat patients with schizophrenia is both practical and safe. Moreover, acupuncture had a positive effect on the BDI-II for the depression group, but acupuncture had no effect on the digit span and on the letter-number sequencing performance for the two clinical groups.
CONCLUSION: The clinical improvement in patients with depression after acupuncture treatment was not accompanied by any significant change in a simple working memory task or in a more complex working memory task; the same was true for the patients with schizophrenia.

1 Introduction

Acupuncture is increasingly used as a complementary medicine treatment for psychiatric illnesses (Samuels, Gropp, Singer, & Oberbaum, 2008). Previous research showed that acupuncture affects mood; a reduction of depressive symptoms in patients with depression after acupuncture treatment was revealed by a meta analysis based on 8 randomized trials (Wang et al., 2008). Recently, researchers have also started to investigate acupuncture for the treatment of schizophrenia (Bosch et al., 2013) and lower positive, negative, and general symptoms in patients with schizophrenia have been reported after acupuncture treatment (Reshef et al., 2013). However, despite its long tradition and wide applications, many questions remain; for instance, is acupuncture able to improve cognitive functioning? In studies on cognitively-impaired animals, acupuncture was found to have a restoration and protection effect (Kim et al., 2009, 2011). Other studies reported improvements in cognitively-impaired patients (Soliman, 2008; Zhong, Su, Liu, & Zhu, 2009).

Therefore, one important cognitive process that will be investigated in the present study is working memory (WM). WM is known to play an important role in higher-level cognitive functioning (Bowles & Salthouse, 2003), like reasoning (Kyllonen & Christal, 1990) and spatial visualization (Salthouse, Babcock, Mitchell, Palmon, & Skovronek, 1990). WM was originally assumed to consist of a central executive that was responsible for monitoring and coordinating two slave systems: the phonological loop and the visuo-spatial sketchpad. The phonological loop temporarily buffers spoken and written material whereas the visuo-spatial sketchpad stores and processes visual or spatial information (Baddeley & Hitch, 1974). Later, the episodic buffer was added as a third slave system and was responsible for linking information across domains to form integrated units of verbal, visual and spatial information with time sequencing (Baddeley, 2000). A recent two-group, randomized, single-blind study on 90 healthy students showed that acupuncture significantly increased WM performance on an automated operation span task in comparison with the control group (Bussell, 2013).

If acupuncture can improve WM performance in healthy participants, it might perhaps also be beneficial for the psychiatric population. For this reason, two long-term (illness duration longer than five years) patient groups that were known to have decreased WM performances, namely, patients with schizophrenia (Mayer, Fukada, Vogel, & Park, 2012) and patients with depression (Christopher & MacDonald, 2005), were investigated by addressing the following research questions: What are the moods of long-term patients with depression or schizophrenia, and what are their WM performances? Also, can acupuncture change mood (Wang et al., 2008) and WM performance (Bussell, 2013) in patients with depression and in patients with schizophrenia?

The first hypothesis is that patients with depression score worse on mood than the patients with schizophrenia and the healthy controls. The second hypothesis is that both patients with schizophrenia and those with depression score worse on WM than the healthy controls. Thirdly, we hypothesize that acupuncture treatment will improve mood in patients with depression and perhaps also in patients with schizophrenia. Fourthly, the WM

performance in patients with schizophrenia and in patients with depression is expected to be improved after acupuncture treatment.

2 Subjects and Methods

2.1 Experimental design

2.1.1 Design

A pragmatic, clinical trial design (MacPherson, 2004) was used to address the effectiveness of acupuncture as a health care intervention in treating patients with schizophrenia or depression in real clinical practice (Godwin et al., 2003).

2.1.2 Acupuncture treatment as clinical intervention

The participants were treated weekly for twelve consecutive treatments. Individualized acupuncture according to traditional Chinese medicine principles was applied after careful diagnosis (Bosch et al., 2013) by a licensed Oriental medical practitioner with more than five years of clinical experience (MacPherson et al., 2002). Needles were left in place for one hour after insertion.

2.1.3 Testing

The tests were completed by the patients in the experimental groups before (T1) and after (T2) acupuncture treatment. For the patients in the waiting-list groups, the tests were also conducted twice, but without treatment. The healthy control participants only completed the test at T1. Testing was conducted in the LVR-Klinik Bedburg-Hau by apprentices that were not informed about the rest of the project.

2.2 Operationalizations

2.2.1 Mood scale

The Becks Depression Inventory-II (BDI-II) (Beck, Steer, & Brown, 1996) was used to measure (depressed) mood (Berna, Lang, Goodwin, & Holmes, 2011; Peirson & Heuchert, 2001). The BDI-II was found to have an excellent test-retest reliability of 0.96 (Sprinkle et al., 2002).

2.2.2 Simple working memory task

The digit-span forward subtask (Wechsler, 2000) was conducted in order to measure WM (Wechsler, 2000). The digit span has a good (0.80) test-retest reliability (Groth-Marnat, 1997).

2.2.3 Complex working memory task

Complex span tasks (Redick et al., 2012), like the letter-number sequencing task (Van den Noort, Bosch, & Hugdahl, 2006), have been developed to measure WM capacity (Redick et

al., 2012), and its norm score was used in the present study (Van den Noort et al., 2006). The test-retest reliability of the letter-number sequencing task was found to be good (0.80) (Groth-Marnat, 1997).

2.3 Sample

Table 1**.**

Participants' demographic information specified for the experimental depression group, the experimental schizophrenia group, the healthy control group, the depression waiting-list group, and the schizophrenia waiting-list group

	Depression Experimental Group *N[1] = 25*	Schizophrenia Experimental Group *N = 25*	Healthy Control Group *N = 25*	Depression Waiting-list Group *N = 25*	Schizophrenia Waiting-list Group *N = 25*
Gender (males/females)	3/22	8/17	7/18	2/23[d]	11/14[d]
Age (in years)	48.68[a] *(10.60)[2]*	41.80 (*10.30*)	38.88[a] *(12.15)*	46.32 *(8.12)*	43.96 *(10.87)*
Length of illness (in years)	7.99[a] *(5.83)*	10.00[b] *(4.30)*	0[ab]	6.75[c] *(5.21)*	10.70[c] *(5.47)*

Note. [1]Number of participants.

[2]Standard deviation.

[a]Significant difference between the experimental depression group and the healthy control group, $p \leq 0.05$.

[b]Significant difference between the experimental schizophrenia group and the healthy control group, $p \leq 0.05$.

[c]Significant difference between the waiting-list depression group and the waiting-list schizophrenia group, $p \leq 0.05$.

In total, 50 patients with schizophrenia and 50 patients with depression were selected by their psychiatrists and asked to participate voluntarily; moreover, 25 healthy control participants entered the study (see Table 1). All patients with schizophrenia were randomly divided into an experimental group and a waiting-list group, as were the patients with depression, and we used the random number generator program in Microsoft Excel for the randomization. The patients in the waiting-list group received no treatment other than their normal psychiatric treatment. According to the 10th revision of the International Classification of Diseases and Related Health Problems (ICD-10) (World Health Organization, 1992), the patients with schizophrenia were diagnosed with schizophrenia F20.0 (paranoid schizophrenia) or F20.5 (schizophrenic residuum), and the patients with depression were diagnosed with depression F33.2 (recurrent depressive disorder, current episode severe without psychotic symptoms). The patients with schizophrenia had a total score of 73.65 (*SD* = 23.43) on the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987). Exclusion criteria were addiction (other than nicotine), epilepsy or other neurological disorders, and other co-morbid psychiatric disorders.

As can be seen in Table 1, no significant gender differences were observed between the three experimental groups (p = 0.222, partial η^2 = 0.041). However, a significant difference in age did exist (see also Table 1) (p = 0.008, partial η^2 = 0.126), and that was due to the fact that the patients with depression were significantly older than the healthy control participants (p = 0.007). As can also be seen in Table 1, the lengths of illness for the patients with depression and the patients with schizophrenia in the experimental groups were not different (p = 0.171, partial η^2 = 0.039). Thus, because both groups had lengths of illness of > 5 years, both could be classified as long-term psychiatric groups (Bosch et al., 2014). An overview of the exact medications used for each individual is given in Table 2. None of the participants had ever received acupuncture treatment. All participants gave written consent, and the ethics committee of the Ärztekammer Nordrhein approved the study beforehand (number 2008331); moreover, the clinical trial has been officially registered under number NTR3132 at the Dutch Trial Register (see also http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=3132). Finally, the study was conducted according to the Declaration of Helsinki (World Medical Organization, 2008).

Table 2.

Overview of the medication used per individual at the start of the study specified for the experimental depression group and the experimental schizophrenia group

Group	**Patients**	**Medication**	**Daily dose**
Depression group	D[1]1	Doxepin Citalopram	2 x 25 mg 1 x 20 mg
	D2	Citalopram	1 x 20 mg
	D3	Trevilor Retard	1 x 150 mg
	D4	Mirtazapin	1.5 x 30 mg
	D5	No medication	No medication
	D6	Zoloft Amineurin	1 x 50 mg 1 x 25 mg
	D7	Zoloft Chlorprothixen	3 x 50 mg 2 x 15 mg
	D8	Citalopram	1 x 20 mg
	D9	Lyrica Doxepin Diazepan	1 x 75 mg 3 x 10 mg 0.5 x 10 mg
	D10	Venlafaxin Retard Venlafaxin Seroquel Prolong Chlorprothixen	1 x 75 mg 1 x 150 mg 2 x 50 mg 2 x 15 mg
	D11	Trevilor Retard	1 x 75 mg
	D12	Doxepin Citalopram	2x 25 mg 1 x 30 mg
	D13	Promethazin Venlafaxin Retard	1 to 2 x 25 mg 1 x 75 mg
	D14	No medication	No medication
	D15	Valdoxan	2 x 25 mg
	D16	Cymbalta Doxepin	1 x 30 mg 1 x 15 mg
	D17	Seroquel Prolong Lamotrigin Abilify	1 x 50 mg and 1 x 150 mg 1 x 50 mg and 1 x 100 mg 1 x 10 mg
	D18	No medication	No medication
	D19	No medication	No medication
	D20	Trevilor Retard Promethazin	1 x 150 mg 1 x 50 mg
	Table continues		

Group	Patients	Medication	Daily dose
Depression Group	D21	Venlafaxin Melneurin	1 x 150 mg 1 x 25 mg
	D22	Valdoxan Circadin	2 x 25 mg 1 x 2 mg
	D23	Citalopram	1 x 20 mg
	D24	Pipamperon Timonil Zoloft	1.5 x 40 mg 3 x 200 mg 3 x 50 mg
	D25	Trenitor Retard	1 x 37.5 mg and 1 x 75 mg
Schizophrenia group	$S^2$1	Zeldox Nipolept Dogmatil Forte Amitriptylin	2 x 20 mg 2 x 50 mg 0.5 1 x 25 mg
	S2	Orifril Solian Zyprexa Velotab	2 x 600 mg 1 x 200 mg 1 x 5 mg
	S3	Zeldox Seroquel Prolong	1 x 60 mg and 1 x 40 mg 1 x 50 mg
	S4	Nipolept Lithium-Ion Zyprexa (Fluanxol)	3 x 25 mg 2 x 12.2 mmol 2 x 7.5 mg (every two weeks 10% 1 ml)
	S5	Zyprexa Velotab	1 x 5 mg and 1 x 10 mg
	S6	Xeplion Levomepromazin	1 x 25 mg 2 x 10 mg
	S7	Seroquel Prolong Seroquel Chlorprothixen (Xeplion)	1 x 400 mg 1 x 100 mg 1 x 50 mg (1 x 100 mg per month)
	S8	Leponex	2 x 100 mg and 1.5 x 25 mg
	S9	Leponex Paroxetin Beta	2 x 100 mg 3 x 10 mg
	S10	Amisulprid Zyprexa Velotab	2 x 400 mg 2 x 10 mg
	S11	Clozapine Beta Dipiperon Ergenyl Chrono Seroquel Citalopram	1 x 25 mg 1 x as-needed 1.5 x 300 mg 2 x 25 mg 1 x 20 mg
	Table continues		

Group	Patients	Medication	Daily dose
Schizophrenia group	S12	Abilify	1 x 10 mg
		Citalogram	0.5 x 20 mg
		Risperdal	1 x 2 mg
		(Xeplion)	(1 x 75 mg per month)
	S13	Pipamperon	0.75 x 40 mg
		Sertralin	3.5 x 50 mg
		Solian	2 x 200 mg
		Trimineurin	3 x 25 mg
	S14	Solvex	0.5 x 4 mg
		Nipolept	2 x 100 mg
		Melperon	25 mg as needed
		Edronax	1 x 4 mg
	S15	Zopiclon	0.5 x 7.5 mg as needed
		Risperdal	2.5 x 2 mg as needed
		Promethazin	1 x 10 mg
		Fluanxol	2 x 5 mg
		Akineton	0.5 x 2 mg
	S16	Zyprexa	1 x 5 mg
		Lihium-Ion	2 x 12.2 mmol
		Nortrilen	3 x 25 mg
		Abilify	1 x 10 mg
	S17	Zeldox	1 x 60 mg and 1 x 40 mg
		Truxal	15 mg up to 3 x daily
		Sertralin	2 x 50 mg
		Seroquel Prolong	1 x 200 mg
		Risperdal	2 x 2 mg
		Lithium-Ion	2 x 12.2 mmol
		Cipralex	1 x 10 mg
		Mirtazapin	1 x 15 mg
	S18	Zeldox	2 x 60 mg
		Seroquel Prolong	1 x 200 mg
		Ergenyl Retard	2 x 500 mg
	S19	Risperdal	2 x 3 mg
		Mirtazapin	1 x 30 mg
		Haldol	3 x 5 mg
		Dominal Forte	1 x 40 mg
		Pipiperon	2 x 40 mg
	Table continues		

Group	Patients	Medication	Daily dose
	S20	Pipamperon Sertralin Solian Trimineurin	0.75 x 40 mg 3.5 x 50 mg 2 x 200 mg 3 x 25 mg
	S21	Zyprexa (Dapotum)	2 x 7.5 mg (every 21 days x 25 mg)
	S22	Solian Clozapin	1 x 400 mg 2.5 x 200 mg
	S23	Clozapin Lamotrigin Risperdal	5 x 25 mg 2 x 50 mg 1 x 2 mg
	S24	Leponex (Haldol)	1 x 50 mg and 1.5 x 25 mg (1 x per month)
	S25	Zyprexa Truxal	1 x 5 mg and 1 x 10 mg 1 x 50 mg

Note. [1]D = Patient with depression.

[2]S= Patient with schizophrenia.

2.4 Acupuncture treatment

2.4.1 Needles

Depending on the place of needling, 0.25 x 25 mm or 0.20 x 15 mm stainless-steel single-use needles (AcuPro C, Wujiang City Cloud & Dragon Medical Device Co., Ltd., China) were used.

2.4.2 Acupuncture points that were used

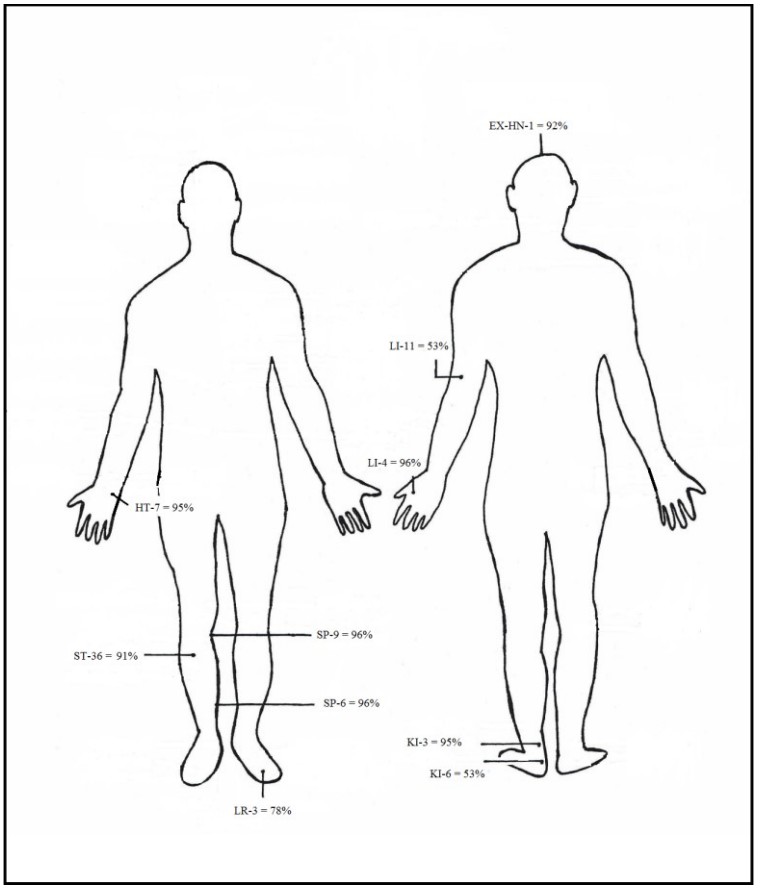

Figure 1a. An overview of the acupuncture points that were most frequently used (> 50%) during the 12 weekly individual acupuncture treatments in the group with depression

An overview of the acupuncture points that were most frequently used (> 50%) during the 12 weekly individual acupuncture treatments is given in Figure 1a for the depression group and in Figure 1b for the schizophrenia group. In total, 56 acupuncture points were used in the depression group, of which the 15 most frequently used points were LI-4 (96%), SP-6 (96%), SP-9 (96%), HT-7 (95%), KI-3 (95%), EX-HN-I (92%), ST-36 (91%), LR-3 (78%), LI-11 (53%), KI-6 (53%), CV-4 (46%), GB-34 (36%), SP-4 (34%), SP-10 (34%), LU-7 (32%), whereas for the schizophrenia group, a total of 61 acupuncture points were used, of which the 15 most frequently used points were EX-HN-I (89%), SP-6 (60%), SP-9 (60%), LI-4 (56%), KI-3 (55%), LR-3 (54%), HT-7 (53%), DU-20 (49%), ST-36 (47%), KI-6 (44%), LI-11 (37%), LU-7 (35%), CV-18 (28%), ST-45 (23%), LI-7 (22%). A complete list of all acupuncture points used per individual treatment and a detailed justification for point selection (Bosch, Staudte, van den Noort, & Lim, 2014) can be obtained from the corresponding author.

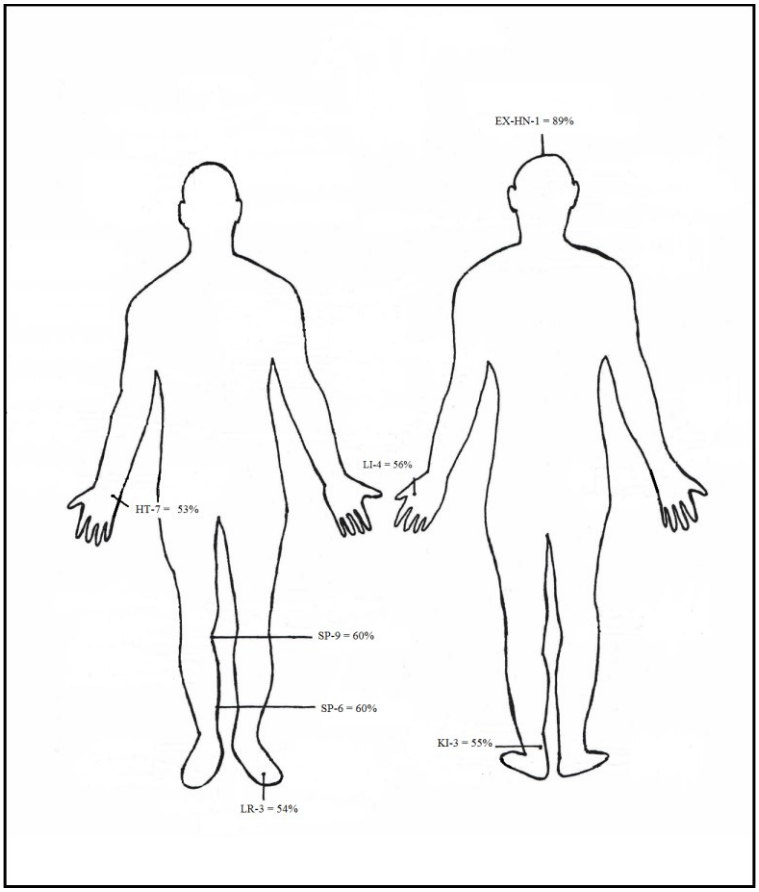

Figure 1b. An overview of the acupuncture points that were most frequently used (> 50%) during the 12 weekly individual acupuncture treatments in the group with schizophrenia

2.5 Analysis design

Before acupuncture treatment (T1), differences between the patients with depression and the patients with schizophrenia in both the experimental and the waiting-list groups and the healthy control participants on the BDI-II (Beck et al., 1996), digit-span forward (Wechsler, 2000), and letter-number sequencing (Van den Noort et al., 2006) were analyzed by using the analysis of variance (ANOVA). For those analyses, first, the patients with depression, patients with schizophrenia, and healthy controls were compared; then, further analyses were conducted for more detailed comparisons. Considering that a relatively large number of patients in the waiting-list groups had dropped out by the end of acupuncture treatment, T2, we decided against a within group factor design. For the psychiatric groups, the results after acupuncture treatment (T2) were also pooled in order to answer the questions whether acupuncture treatment improved mood in a psychiatric population and whether group (treatment and waiting-list groups) differences existed. Next, paired t tests were used to establish within group effects. Because of the difference in age that existed

between the depression and the healthy control groups, an analysis of covariance (ANCOVA) was conducted in order to determine if the results were affected by this variable.

3 Results

3.1 Mood

The analysis (ANOVA) of the BDI-II scores at the baseline (T1) showed a significant difference in total BDI-II score between the depression group, the schizophrenia group, and the healthy control group (p = 0.000, partial η^2 = 0.676). As can be seen in Table 3, patients with depression had higher BDI-II scores than both patients with schizophrenia (p = 0.000) and healthy control participants (p = 0.000); moreover, patients with schizophrenia had higher BDI-II scores than healthy control participants (p = 0.000).

After acupuncture treatment (T2), the patients with depression still had higher scores than the patients with schizophrenia (p = 0.000, partial η^2 = 0.456). With respect to the "acupuncture effect" (i.e., before versus after acupuncture treatment), the analysis of the total psychiatric group scores (which was used in order to maintain as much statistical power as possible) on the BDI-II showed that those scores were significantly lower after acupuncture treatment (p = 0.027, partial η^2 = 0.058). An analysis (ANCOVA) revealed that age did not have a significant influence on this result (p = 0.170, partial η^2 = 0.023), nor did length of illness (p = 0.057, partial η^2 = 0.046). Moreover, the analysis of the waiting-list groups revealed that the total psychiatric group effect after acupuncture could not be explained by the fact that the participants were tested twice (p = 0.429, partial η^2 = 0.008). Finally, when the depression and the schizophrenia groups were analyzed separately, the patients with depression show significantly lower BDI-II scores after acupuncture treatment (p = 0.014, partial η^2 = 0.141), but the patients with schizophrenia did not (p = 0.121, partial η^2 = 0.059).

Table 3.

Overview of the mean BDI-II scores and the corresponding standard deviations at baseline (T1) specified for the depression group, the schizophrenia group, and the healthy control group. Moreover, for the depression group and the schizophrenia group, an overview of the BDI-II scores after acupuncture treatment (T2) is given. In addition, the mean BDI-II scores and the corresponding standard deviations of the waiting-list groups for the first testing (T1) and for the second testing (T2) are given

Scale	T1 (BEFORE ACUPUNCTURE)			T2 (AFTER ACUPUNCTURE)		T1 (WAITING LIST)		T2 (WAITING LIST)	
Group	Depression Group *N[1] = 25*	Schizophrenia Group *N = 25*	Healthy Control Group *N = 25*	Depression Group *N = 17*	Schizophrenia Group *N = 17*	Depression Group *N = 25*	Schizophrenia Group *N = 25*	Depression Group *N = 16*	Schizophrenia Group *N = 10*
BDI-II[3]	30.48[abd] *(9.06)[2]*	14.12[ac] *(10.70*)	2.12[bc] *(2.37)*	23.00[d] *(7.83)*	9.35 *(7.54)*	25.04 *(11.43)*	17.52 *(13.74)*	21.56 *(11.34)*	14.60 *(9.89)*

Note. [1]Number of participants.

[2]Standard deviation.

[3]BDI-II = Becks Depression Inventory.

[a]Significant difference between the experimental depression group and the experimental schizophrenia group, $p \leq 0.05$.

[b]Significant difference between the experimental depression group and the healthy control group, $p \leq 0.05$.

[c]Significant difference between the experimental schizophrenia group and the healthy control group, $p \leq 0.05$.

[d]Mean BDI-II score at T1 is significantly different ($p \leq 0.05$) from the mean BDI-II score at T2.

3.2 Simple working memory task

An analysis (ANOVA) of the digit-span scores at baseline (T1) showed significant differences between the depression group, the schizophrenia group, and the healthy control group (p = 0.003, partial η^2 = 0.148). As can be seen in Table 4, patients with depression had lower digit-span scores than healthy control participants (p = 0.002), but their scores did not differ from the scores of patients with schizophrenia (p = 0.181). Moreover, no differences in digit-span scores were found between the patients with schizophrenia and the healthy control participants (p = 0.278). After acupuncture treatment (T2), the scores of the patients with depression again did not differ from the scores of the patients with schizophrenia (p = 0.949, partial η^2 = 0.000).

With respect to the “acupuncture effect”, an analysis of the total psychiatric group scores before versus after acupuncture treatment showed no significant differences (p = 0.528, partial η^2 = 0.005). Similarly, non-significant results on the digit-span tasks performed before and after acupuncture treatment were found when the depression group (p = 0.194, partial η^2 = 0.039) and the schizophrenia group (p = 0.740, partial η^2 = 0.003) were analyzed separately.

Table 4.

Overview of the mean scores on the digit span task and the corresponding standard deviations at baseline (T1) specified for the depression group, the schizophrenia group, and the healthy control group. Moreover, for the depression group and the schizophrenia group, an overview of the digit span scores after acupuncture treatment (T2) is given. In addition, the mean scores on the digit span task and the corresponding standard deviations of the waiting-list groups for the first testing (T1) and for the second testing (T2) are given.

Scale	T1 (BEFORE ACUPUNCTURE)			T2 (AFTER ACUPUNCTURE		T1 (WAITING LIST)		T2 (WAITING LIST)	
Group	Depression Group *N*[1] = 25	Schizophrenia Group *N = 25*	Healthy Control Group *N = 25*	Depression Group *N = 20*	Schizophrenia Group *N = 20*	Depression Group *N = 25*	Schizophrenia Group *N = 23*	Depression Group *N = 16*	Schizophrenia Group *N = 8*
Digit span task	8.28[a] *(1.97)*[2]	9.28 (*1.90)*	10.16[a] *(1.77)*	9.10 *(2.20)*	9.05 *(2.70)*	9.00 *(2.65)*	9.26 *(1.76)*	9.00 *(2.45)*	8.38 *(2.77)*

Note. [1]Number of participants.

[2]Standard deviation.

[a]Significant difference between the experimental depression group and the healthy control group, $p \leq 0.05$.

3.3 Complex working memory task

An analysis (ANOVA) of the scores on the letter-number sequencing task at baseline (T1) showed significant differences in those scores between the depression group, the schizophrenia group, and the healthy control group (p = 0.000, partial η^2 = 0.192). The patients with schizophrenia scored significantly lower than both the patients with depression (p = 0.025) and the healthy control participants (p = 0.000); the data are presented in Table 5. This difference between two psychiatric groups had vanished by the end of acupuncture treatment (T2) (p = 0.122, partial η^2 = 0.062).

With respect to the "acupuncture effect" (i.e., before versus after acupuncture treatment), the analysis of the total psychiatric group scores before versus after acupuncture treatment showed no improvements after acupuncture treatment (p = 0.264, partial η^2 = 0.014). Finally, the analysis of the subgroups after acupuncture treatment did not reveal significant differences on the letter-number sequencing task for the depression group (p = 0.719, partial η^2 = 0.003) and for the schizophrenia group (p = 0.178, partial η^2 = 0.042).

Table 5.

Overview of the mean scores on the letter-number sequencing task and the corresponding standard deviations at baseline (T1) specified for the depression group, the schizophrenia group, and the healthy control group. Moreover, for the depression group and the schizophrenia group, an overview of the mean scores on the letter-number sequencing task after acupuncture treatment (T2) is given. In addition, the mean scores on the letter-number sequencing task and the corresponding standard deviations of the waiting-list groups for the first testing (T1) and for the second testing (T2) are given.

Scale	T1 (BEFORE ACUPUNCTURE)			T2 (AFTER ACUPUNCTURE)		T1 (WAITING LIST)		T2 (WAITING LIST)	
Group	Depression Group *N[1] = 25*	Schizophrenia Group *N = 25*	Healthy Control Group *N = 25*	Depression Group *N = 20*	Schizophrenia Group *N = 20*	Depression Group *N = 25*	Schizophrenia Group *N = 22*	Depression Group *N = 16*	Schizophrenia Group *N = 8*
Letter-number sequencing task	9.44[a] *(3.73)[2]*	7.12[ab] (*2.52*)	10.60[b] *(2.68)*	9.80 *(2.71)*	8.30 *(3.26)*	10.32 *(4.02)*	6.95 *(3.32)*	10.81 *(3.64)*	7.38 *(2.62)*

Note. [1]Number of participants.

[2]Standard deviation.

[a]Significant difference between the experimental depression group and the experimental schizophrenia group, $p \leq 0.05$.

[b]Significant difference between the experimental schizophrenia group and the healthy control group, $p \leq 0.05$.

4 Discussion

This pragmatic, clinical trial (MacPherson, 2004) investigated mood (Wang et al., 2008) and WM (Bussell, 2013) in a psychiatric sample and attempted to determine if acupuncture might be able to improve mood and WM. Differences were found between the psychiatric groups and the healthy control group, but not on all measures. The most relevant acupuncture outcome was that acupuncture treatment significantly improved BDI-II (Beck et al., 1996) scores in patients with depression.

We confirmed the low BDI-II scores for the depressed population, and interestingly, the patients with schizophrenia showed signs of better mood, although their average score was still below what is considered clinically relevant. In line with our hypothesis, after 12 weeks of acupuncture treatment, patients with depression reported an improved mood on the BDI-II, which is one of the most widely used instruments for measuring the severity of depression (Joe, Woolley, Brown, Ghahramanlou-Holloway, & Beck, 2008). Moreover, previous research has shown that the BDI-II has excellent test-retest reliability (Sprinkle et al., 2002). This finding and our waiting-list results (i.e., no significant difference in BDI-II between two measurements) are further support for the hypothesis that the different scores before and after acupuncture treatment are a result of the acupuncture intervention. This finding is in line with previous acupuncture research on depression and confirms that acupuncture is effective in reducing depressive symptoms (Lyons, van der Watt, Shen, & Janca, 2012). In contrast to the depression group, and against our hypothesis, however, the patients with schizophrenia did not show lower BDI-II (Beck et al., 1996) scores after acupuncture treatment. An explanation for their stable mood might be the fact that the patients with schizophrenia have much lower scores on the BDI than the depressed group, M = 14.12 versus M = 30.48, so those patients do not have much room for improvement. This is in sharp contrast to the data on the patients with depression who had plenty of room for improvement as a result of acupuncture. Nevertheless, as can also be seen in Table 3, both experimental groups show a reduction of more than 4.5 points in the total BDI-II score, and although this result may not be significant for the group with schizophrenia, it may have clinical relevance, particularly for the individual patient in daily clinical practice, and warrants further research.

As can be seen in Table 4, the WM results showed that, at baseline, only the patients with depression scored lower than the healthy controls on the simple WM task; the patients with schizophrenia surprisingly scored within the normal range. This was not expected because research has shown that patients with schizophrenia show relatively stable problems within broad neurocognitive domains (Corigliano et al., 2014), and evidence even exists for ongoing neurocognitive deterioration as the disease progresses (Corigliano et al., 2014). Moreover, cognitive dysfunction is seen as a biomarker that is even visible in healthy relatives of patients with schizophrenia (Lett, Voineskos, Kennedy, Levine, & Daskalakis, 2014). On the other hand, patients that have been ill for a long time have been studied less, which might

explain the unexpected performance (Herold et al., 2015). In contrast to our hypothesis, the scores on the digit span did not change after acupuncture treatment, showing that acupuncture did not influence performance on a simple WM task. The reason for this might be that the baseline scores (particularly for the schizophrenia group) were already in the normal range, and as a result, acupuncture could not further improve them.

The results of the complex WM task revealed that, at baseline, as we expected, the patients with schizophrenia performed worse on the letter-number sequencing task (Van den Noort et al., 2006) than both the patients with depression and the healthy controls (see also Table 5); however, surprisingly, the patients with depression did not perform worse than the healthy controls. More importantly, after acupuncture treatment, no WM improvements were found in both clinical groups. Future research with a more complex WM task (such as the reading-span task (Van den Noort, Bosch, Haverkort, & Hugdahl, 2008)) is needed in order to exclude the possibility that the letter-number sequencing task, which was used in the present study, did not tap enough processing elements (in addition to the storage elements) (Van den Noort et al., 2008), and as a result, no effect of acupuncture on the complex WM task could be found.

One of the possible mechanisms of action is that the (beneficial) effect of acupuncture in depression may work via the neurotransmitters dopamine, norepinephrine, and serotonin; neurotransmitters that are often reported in the literature because of their role in depression (Dunlop & Nemeroff, 2007; Nutt, 2006; Young, 2007). Previous research found evidence for the fact that in cases of shortage, acupuncture causes the release of dopamine, norepinephrine, and serotonin (Chang, Hsieh, & Cheng, 1996; Han, 1986; Lee et al., 2002). As a result, a modulating and normalizing effect occurs (Bosch, Van den Noort, Staudte, & Lim, 2015), leading to a decrease of depressive symptoms (Zhang, Chen, Yip, NG, & Wong, 2010). Another possible mechanism of action is that the (beneficial) effect of acupuncture in depression might work via an indirect working mechanism, namely the improvement of sleep (Bosch et al., in press). Sleep disorders are often reported in patients with depression or schizophrenia (Bosch et al., 2012); moreover, sleep was found to improve after acupuncture in patients with depression or schizophrenia (Bosch et al., 2013; Reshef et al., 2013). Future research on those possible mechanisms of action is needed in order to firstly explain the (beneficial) effect of acupuncture in depression that is reported in the literature (Zhang et al., 2010) and was found in the present study and secondly, why no beneficial effect of acupuncture was found in schizophrenia in this study. Perhaps the effects of strong medication use of the patients with schizophrenia with the acupuncture treatment may be an explaining factor. Especially in typical antipsychotics, dopamine D2 receptors are blocked (Seeman, 2002), thereby possibly interfering the mechanism of acupuncture.

The present study has several limitations. For instance, based on the present study, how long the improved mood in patients with depression lasts after finishing the acupuncture treatment is unclear. Future studies (with follow-up measurements) on the clinically relevant long-term effects of acupuncture treatment are, therefore, needed (Carlsson, 2002). Another limitation of our study is that all participants were on medication during the study (see also

Table 2), and medications could not be stopped due to ethical reasons (Fulford & Howse, 1993) (raised by the ethics committee of the Ärztekammer Nordrhein). Finally, the sample sizes in the present study are relatively small (Streiner, 1990) due to practical reasons (Patel, Doku, & Tennakoon, 2003). Therefore, in future research, larger clinical groups need to be investigated in multiple-center studies.

5 Conclusions

The clinical improvement in the patients with depression after acupuncture treatment was not accompanied by significant changes in either a simple or a more complex working memory task; the same was true for patients with schizophrenia.

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Chapter 7

A case study on acupuncture in the treatment of schizophrenia

Based on:

Bosch, P., Staudte, H., Van den Noort, M., & Lim, S. (2014). A case study on acupuncture in the treatment of schizophrenia. *Acupuncture in Medicine, 32*(3), 286–289. doi:10.1136/acupmed-2014-010547

ABSTRACT

This report describes the use of acupuncture as an add-on treatment for a chronic patient with schizophrenia. The 63 year old female patient suffered from persistent hallucinations and even physical pain, as a result of the hallucination of a black bird that kept pecking her back. The patient received 12 weekly acupuncture treatments. A clinical diagnostic interview and psychological testing (on sleep quality, depression, and on positive and negative symptoms) were conducted before, immediately after, and three months after the acupuncture treatment. The results of the diagnostic interview gave important insights in the treatment effects. The patient experienced improved daily functioning and noticed a change in hallucinations. Although the hallucinations still occurred, she felt less disturbed by the hallucinations. Interestingly, the pain decreased markedly. In addition, the results show that the overall score of the positive and negative symptoms did not change immediately; however, a decrease in symptoms occurred three months after acupuncture treatment. Moreover, the patient described an immediate improvement of sleep; this was confirmed by a daytime sleepiness questionnaire. Interestingly, the patient was not able to fill in a (longer) test on sleep quality beforehand, but could fill it in after the treatment period. Finally, a delayed improvement in the depression scale was found. Although larger clinical intervention studies on acupuncture and schizophrenia are needed, the results of this case study indicate that acupuncture may be beneficial as an add-on treatment tool in patients with schizophrenia.

INTRODUCTION

Acupuncture is increasingly used in Western medicine as an add-on treatment for various psychiatric diseases (Bosch et al., 2013), particularly in the treatment of patients with depression (Andreescu, Glick, Emeremni, Houck, & Mulsant, 2011). However, the use of acupuncture in patients with schizophrenia is rare (Schmid & Brunisholz, 2006). We report a case from a large German psychiatric clinic. We were interested in examining if acupuncture was helpful as an add-on treatment in a patient with schizophrenia, and assessed which psychological tests were suitable to capture the effects of the acupuncture treatment.

CASE DESCRIPTION

In November 2003, our patient (aged 56 years) experienced compulsory admission to a psychiatric clinic for the first time. This was necessary to prevent danger to the patient and others due to severe delusions. The psychotic symptoms were disrupted only after she was compulsorily injected with a high dose of neuroleptics. After she left the psychiatric clinic she received regular treatment as an outpatient for several years, and her situation was continually characterised by significantly decreased performance, exhaustion, increased psychophysical vulnerability, reduced concentration, and reduced attention. She showed increasing periods of extreme tiredness and mentioned pain in the back, legs, shoulders, and ribs in particular. She described the pain as resulting mainly from one of her hallucinations; a black bird that kept pecking at her back, which caused the pain. Moreover, she spoke of the bird that continually sat next to her and kept swearing and calling her names. As a result of her continued suffering, the patient decided to participate in an acupuncture project. The study was approved by the ethical committee of the Ärztekammer Nordrhein. The patient drank about 2 litres of coffee a day (sometimes more) and smoked heavily.

Medication

The patient was on medication during the whole of the study period. She used Melperone 75 mg at night, Risperdal 3 mg daily dose (1 mg in the morning, afternoon, and evening), and Risperidone 37.5 mg every 14 days.

Psychological investigation

To measure the severity of her schizophrenic symptoms, the Positive and Negative Symptom Scale (PANSS) (Kay, Fiszbein, & Opler, 1987) was used (including the cognitive component) (Lindenmayer, Bernstein-Hyman, & Grochowski, 1994). The results showed that the patient was suffering from serious positive and negative symptoms and from general psychopathology at the start of the study. The Epworth Sleepiness Scale (Johns, 1991) which measures subjective experience of daytime sleepiness, revealed that she was very sleepy during the day. Before treatment, she was not able to complete the Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) that measures sleep quality and possible disturbances in sleep patterns during the previous month. She was too

disturbed by her increasing hallucinations and asked whether it was possible to skip the test. Finally, the severity of depressive symptoms was measured with the Becks Depression Inventory II (BDI-II) (Beck, Steer, & Brown, 1996). The patient's score was 27, showing that she was suffering from moderate depression at the beginning of the study.

Treatment and outcome

The patient was given individualised acupuncture treatment once a week for twelve weeks and points were punctured bilaterally. The needles used were 0.25 x 25 mm or 0.20 x 15 mm stainless steel (depending on the place of needling) single use needles (AcuPro C, Wujiang City Cloud & Dragon Medical Device Co., Ltd., China) and were placed according to TCM principles. *De qi* was obtained and the needles were not stimulated after that, but left in place for one hour.

Acupuncture diagnosis and point selection

Due to the thin, (mostly) pale, flaccid, (mostly) moist tongue with many cracks and hardly any coating, and the weak and sometimes rapid pulse, a Qi and Blood deficiency was diagnosed. From time to time, local stagnation of Qi and Blood presented as a purple colour of the tongue and lips (and an increase in pain related to hallucinations) together with some heat symptoms (noticeable foremost in the pulse in the Spleen/Stomach position and then in the stronger pulse). Although she mostly presented with symptoms of depletion, there were also symptoms of excess (Phlegm misting the Mind or even at some point Fire harassing the Mind). In addition, years of heavy medication (continuing during treatment), and coffee and cigarette consumption were taken into consideration, as also reported by others (Ronan, Harbinson, MacInnes, Lewis, & Robinson, 2010). A careful individual diagnosis (at each treatment) was conducted by a licensed oriental medical practitioner with more than five years of clinical experience (Bosch et al., 2013).

RESULTS

Figure 1 provides an overview of the acupuncture points used (and the frequency). Treatment was based on the following primary points: LI4, LI11, ST8, ST36, SP6, SP9, BL67, KI3, LV3, DU20, and EX-HN1 (*Sishencong*) (detailed justification for point selection can be obtained from the author).

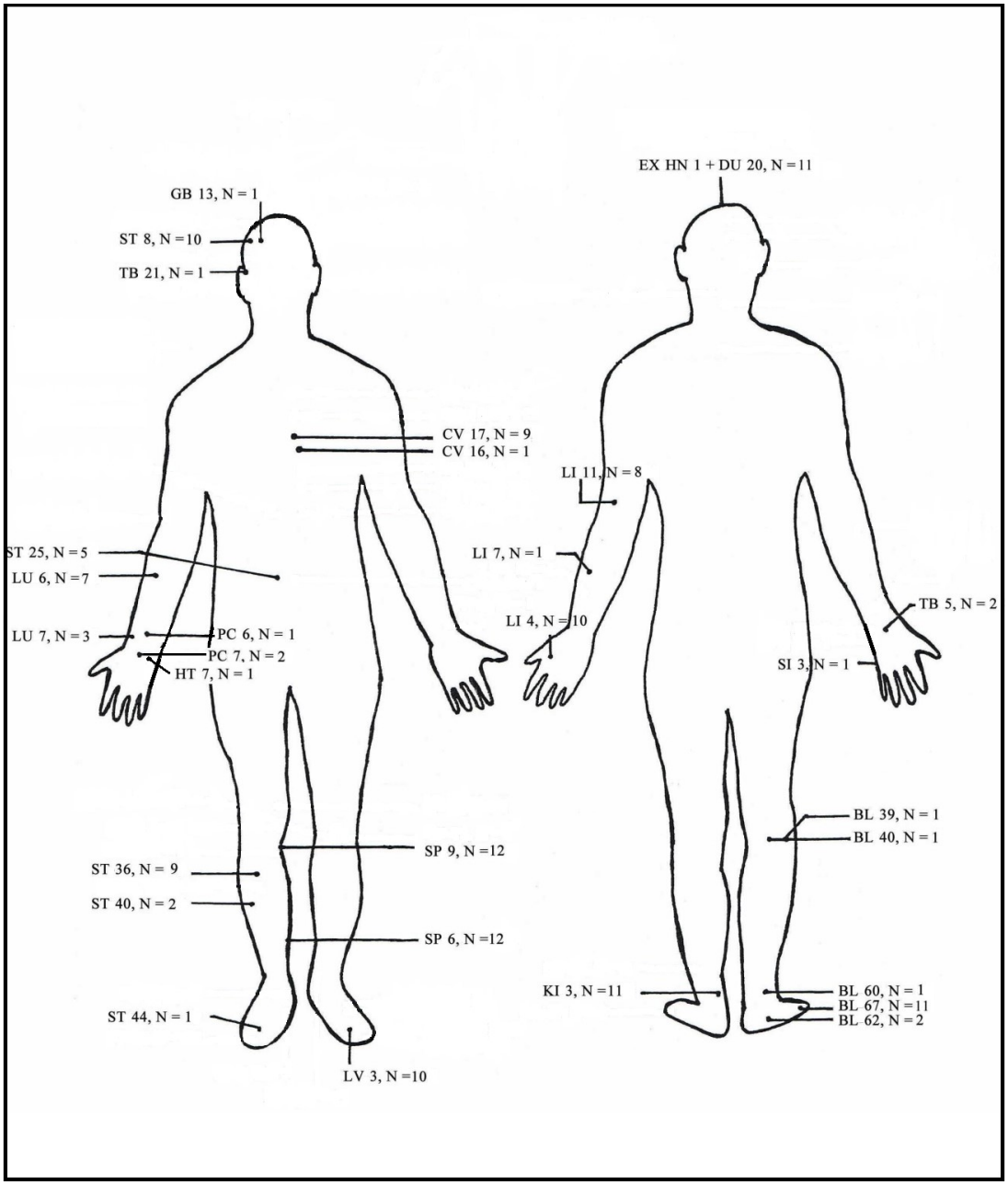

Figure 1. *An overview of the acupuncture points (and frequency) that were used during 12 weekly acupuncture treatments.*

The diagnostic interview gave important insights into the treatment effects of a patient suffering from schizophrenia and persistent hallucinations. She experienced better daily functioning and noticed a change in hallucinations. Although the black bird was still sitting next to her, he did not speak during the first three days after treatment and he did not pick her back. Her pain and suffering therefore, decreased markedly during those three days and she was able to sleep. At the end of the three days, the bird started to swear again and took up his usual pecking, causing the same pain as before. This happened in the same way, 12 weeks in a row.

Table 1.

Psychological test results of the patient with schizophrenia on the Epworth, PANSS, BDI, and PSQI before and after acupuncture treatment and at follow-up.

Test	Before Acupuncture	After Acupuncture	Follow-Up
PANSS cognitive	7	7	6
PANSS positive	14	20	16
PANSS negative	16	16	10
PANSS psychopathology	39	34	30
PANSS total	69	70	56
Epworth	12	6	13
PSQI total	-	8	12
BDI	27	28	24

Note. - Means that it was not possible to conduct the psychological test in the patient with schizophrenia, due to increased hallucinations when she started to read the text.

Table 1 shows the results of the psychological testing. The overall score for positive and negative symptoms did not change directly after acupuncture treatment, indicating that her psychiatrist (not involved in the project) did not notice large differences. However, three months after acupuncture treatment a large effect was noted (70 versus 56), and this was the case for all three subscales of the PANSS. The most striking result was found on the PANSS negative subscale (a decrease from 16 to 10), meaning that the number of negative symptoms decreased. The PANSS positive (a decrease from 20 to 16) and the PANSS psychopathology (a decrease from 34 to 30) show similar results, implying that the number of positive symptoms decreased and the amount of psychopathology was also decreased.

Moreover, the score on the Epworth Sleepiness Scale showed less sleepiness after acupuncture; however, three months after the acupuncture treatment this beneficial effect is back to the level before the acupuncture treatment. The results of the PSQI showed that our patient was not able to complete the questionnaire before treatment. She responded with increased hallucinations and could not continue filling it in. After treatment, she experienced no problems with the list and we found a total score of eight, indicating poor sleep quality (Six is increasingly seen as the cut-off score for good sleep quality, Hametner et al., 2012). Three months after acupuncture treatment, however, sleep quality had decreased. The total score on the PSQI increased to 12, which can be characterised as very poor sleep quality and the patient described this as the way as before treatment.

No differences were found on the depression scale, indicating that her depressed mood did not improve directly after acupuncture treatment; however, a small improvement is noticeable at follow up.

DISCUSSION

The results of this case study indicate that acupuncture may be beneficial as an add-on treatment tool for patients with schizophrenia, as a number of positive and negative symptoms decreased three months after acupuncture treatment and it appeared to have an effect on sleep and daytime sleepiness. The results of this case study seem to support the idea that one of the underlying treatment mechanisms of acupuncture in schizophrenia is an indirect one, namely through improving sleep (which is what the patient described). From a Western point of view, it seems logical that when patients sleep better, their concentration improves and they feel better. Interestingly, previous neuroimaging research revealed that the "limbic-paralimbic-neocortical network", consisting of the amygdala, hypothalamus, and default mode network, is involved in response to acupuncture. These areas are known for their role in the regulation of sleep and wakefulness; moreover, it was found that acupuncture had a modulating and normalising effect on these areas (Hui, Marina, Liu, Rosen, & Kwong, 2010).

However, larger studies on acupuncture and schizophrenia are needed (Rathbone & Xia, 2005) in order to test the effectiveness of acupuncture in schizophrenia and to unravel the possible underlying working mechanisms. To date, a systematic review (Lee, Shin, Ronan, & Ernst, 2009) on thirteen studies showed only limited evidence for the effectiveness of acupuncture in treating the symptoms of schizophrenia. In future studies, care should be given to the type of psychological tests used to measure effects within this group. Due to the hallucinations present, long tests are unsuitable. Moreover, in the study design, the short-term and long-term effects of acupuncture should be considered. Our patient would likely have given different answers on, for example, a pain scale, during the first three days immediately following acupuncture treatment, compared with after those three days. Moreover, although the patient described having fewer problems, due to the fact that her bird sat silently, it was still there, probably causing less difference on the PANSS, since she was still hallucinating.

CONCLUSION

This case report suggests that acupuncture may be a suitable add-on treatment in patients with chronic schizophrenia, visible in the lower number of positive and negative symptoms, improved daytime sleepiness, and improvement in mood. Acupuncture may also change the hallucinations themselves; the hallucinations still occurred, but the pain and distress caused by the hallucinations decreased markedly.

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Chapter 8

Schizophrenia, depression, and sleep disorders: Their traditional oriental medicine equivalents

Based on:

Bosch, P., De Rover, P., Staudte, H., Lim, S., & Van den Noort, M. (2015a). Schizophrenia, depression, and sleep disorders: Their traditional oriental medicine equivalents. *Journal of Acupuncture and Meridian Studies, 8*(10), 17–21. doi:10.1016j.jams.2014.06.001

Abstract

Psychiatric disorders can be described and treated from both a Western (allopathic) and an Eastern perspective, which should be taken into account when conducting research. Patients with schizophrenia or depression are likely to be undergoing Western treatment when they are referred to an acupuncturist for (add-on) treatment, and knowledge of both types of treatments is necessary to integrate them successfully. In this study, the different Traditional Oriental Medicine (TOM) diagnostic patterns in patients with a Western diagnosis of schizophrenia, depression, or sleep disorders are described from a literature and a clinical perspective. The data on 30 depression and 30 schizophrenia patients from a German study are presented. Our results show that if a psychiatric group, sorted in accordance to Western diagnostic principles, is diagnosed on the basis of TOM diagnostic patterns, it can be categorized into different groups of patients with psychiatric disorders; this finding has far-reaching consequences in scientific research on acupuncture. Moreover, we found a high prevalence of sleep disorders in patients with both schizophrenia and depression, which could be explained from a TOM diagnostic patterns perspective. Finally, we discuss sleep quality as a treatment objective that may play a crucial role in mediating acupuncture-induced treatment effects in patients with schizophrenia and depression.

1. Introduction

Psychiatric disorders can be described from both a Western (allopathic) and an Eastern perspective. In particular, patients with a Western diagnosis of schizophrenia or depression are likely to be undergoing Western treatment when they are referred to an acupuncturist for (add-on) treatment; therefore, knowledge of both types of treatments is needed for integrating them. Sleep disorders are comorbid with most psychiatric disorders. It is well known that sleep disorders occur in depression, but they are often underestimated in schizophrenia (Bosch et al., 2012). Research on acupuncture and depression is more difficult than one might think because of the fact that, although patients seem to have the same Western diagnosis, they have different Traditional Oriental Medicine (TOM) diagnostic patterns, creating a heterogeneous group. From a TOM point of view, some patterns are more severe than others, making it logical that acupuncture results differ between the various patient groups within the overall group of patients with depression. In patients with schizophrenia, this is even more extreme because this patient group is already heterogeneous from a Western point of view. Moreover, if standardized treatments are used, these may be more suitable for some patterns than for others. Therefore, in order to further illustrate this point, we discuss the results from two different psychiatric groups (patients with schizophrenia and those with depression), in order to anser the following research questions: what TOM diagnostic patterns can be distinguished in patients who would receive a Western diagnosis of schizophrenia, depression, or sleep disorders; how are these disorders related; and how can acupuncture treatment results be explained both from an Eastern and a Western perspective (Bosch & van den Noort, 2008)?

2. Materials and methods

Thirty patients with schizophrenia and 30 patients with depression participated in this study. All patients were outpatients at the LVR-Klinik Bedburg-Hau, which is a large psychiatric clinic in Germany. The patients with schizophrenia were diagnosed with schizophrenia F 20.0 (paranoid schizophrenia – 28 patients) or F20.5 (schizophrenic residuum – two patients), and the patients with depression were diagnosed with depression F33.2 according to the ICD-10 (World Health Organization, 1992). Of the 30 patients with schizophrenia, 13 were males and 17 were females, and of the 30 patients with depression, three were males and 27 were females. Note that it is common in Western Medicine (WM) that significantly more female han male patients represent with depression (Schuch, Roest, Nolen, Penninx, & de Jonge, 2014). Patient ages were within the range of 19 – 62 years (mean age = 42.90 years, *SD* = 10.34 years) for the schizophrenia group and from 34 – 64 years (mean age = 49.60 years, *SD* = 7.51 years) for the depression group. Moreover, the mean duration of illness was 11.40 years (*SD* = 6.73 years) for the schizophrenia group with a minimum of 1 year and a maximum of 26 years, and 8.00 years (*SD* = 6.79 years) for the depression group, with a minimum of 1 year and a maximum of 30 years. None of the participants had ever

experienced acupuncture treatment previously. Oral and written informed consent were obtained from all participating adult subjects, and all of them signed a consent form. The ethics committee of the Ärztekammer Nordrhein approved the study beforehand; moreover, the study was conducted according to the Declaration of Helsinki (World Medical Organization, 1996). The *Standard Acupuncture Nomenclature* (http://www.wpro.who.int/publications/ pub_9290611057.htm) and the *WHO International Standard Terminologies on Traditional Medicine in the Western Pacific Region* (http://www.wpro.who.int/ publications/PUB_9789290612487.htm) published by the World Health Organization Regional Office for the Western Pacific were used in our study.

In TOM, schizophrenia is seen in the context of depression-mania (diān-kuáng). As early as during the Ming Dynasty, Lǐ Chān stated the following in Yī Xué Rù Mén: “Mania patients are ferociously mad. In mild cases they act self-important and self-righteous, and they like to sing and like to dance; in more serious cases they throw off their clothes and run amok, climb walls and mount the roof. In even more serious cases they beat their head (against a wall) and scream, are negligent around fire and water, or can have inclinations to murder. This naturally results from inordinate exuberance of the Heart Fire, a superabundance of Yang Qi, the spirit failing to keep to its abode, and Phlegm-Fire congestion and exuberance. The crux of treating mania is to descend Phlegm and down bear Fire” (Dey, 1999, p.2). During the Tang Dynasty, Sūn Sī Miǎo stated the following in Qiān Jīn Yào Fāng: “When wind enters the Yin channels, there is withdrawal (diān). The forms can have many extremes. (Some patients) are taciturn and make no sound, (while others) say many things in effusive speeches. They also may sing or cry, moan or laugh. They may also sleep or sit in ditches, eat feces and filth, show their naked bodies (in public), move around all day and night, and ceaselessly curse and cuss” (Dey, 1999, p. 2).

Patients with schizophrenia often have symptoms of both kuάng and diān illnesses. Their diān symptoms include problems in persistence, less self motivation, feeling less up for society, deep silence/mutism, weakness in answering questions, problems in forming an opinion about their surroundings, and disinterest in their own appearances. These patients have what Western medicine calls negative symptoms, and they seem to be absent. They can also show kuάng behavior, such as excited movements, disordered speech, explosive behavior and spontanious outbursts in which things are destroyed or people are hurt (Dey, 1999, pp. 2–3). In TOM, bipolar disorders are often described as Diān and Kuάng (‘mania and withdrawal’). ‘Mania’ means a hyperactive state in which a patient is excited; the state is characterized by loud, inappropriate and possibly aggressive behavior. Mania is mainly caused by a hyperactivity of Yang-Qi caused by several patterns, such as Fire because of Qi stagnation or empty heat due to Yin deficiency. ‘Withdrawal’ means a state of emotional depression, loss of interest, and loss of appetite and reduced fluid intake (Dey, 1999, p. 9). As can be seen in Table 1, several patterns can be distinguished in patients who receive a

Western diagnosis of schizophrenia. Table 1 was created based on information from several textbooks (Flaws & Lake, 2001; Maciocia, 2005).

Table 1.
Patterns that might receive a Western diagnosis of schizophrenia (Flaws & Lake, 2001; Maciocia, 2005).

Yang illness/excess pattern (Acute phase)
Yin illness/excess pattern
Liver Qi stagnation with or without Liver-Blood stasis
Liver-Blood heat
Liver-Fire
Qi deficiency
Qi and Blood deficiency
Phlegm and Qi stagnation (with Qi emptiness)
Internal Pleghm/Dampness, causing an obstruction
Phlegm (and) Fire that attack the upper body/Phlegm heat harassing the mind
Phlegm misting the mind
Heart-Spleen deficiency
Heart-Blood heat
Heart-Blood stasis
Heart-Fire
Heart-Yin deficiency (with or without empty heat)
Heart and Kidney Yin deficiency with Heart empty-heat
Stomach and Heart Phlegm-Fire
Yang emptiness with Spleen and Kidney deficiency (including phlegm)
Kidney Essence deficiency
Yin deficiency not controlling fire
(Internal) Blood stasis
Stasis of Blood in the Lower Burner

From a TOM point of view, almost all patients who suffer from depression from a western point of view present Liver Qi stagnation, however, mostly this stagnation is complicated by Stomach disharmony, empty heat, Spleen and/or Blood deficiency, Yin and/or Yang deficiency, Phlegm, Dampness, etc. As can be seen in Table 2 (Flaws & Lake, 2001; Maciocia, 2005), several patterns can be distinguished in patients that might have received a diagnosis of depression accoriding to WM.

Table 2.

Patterns that might receive a Western diagnosis of depression (Flaws & Lake, 2001; Maciocia, 2005).

Liver Qi depression and binding
Liver depression transforming Fire
Liver Blood deficiency
Liver Yin deficiency (with empty heat)
Liver-Fire
Blood movement depression and stagnation
Phlegm misting the Mind
Phlegm Qi depression and binding
Phlegm Fire (obstructing the Qi)
Depression causing detriment to the Heart Qi
Heart-Spleen dual vacuity
Heart & Lung Qi stagnation
Heart-Blood deficiency
Heart-Yin deficiency
Stomach and Heart Phlegm-Fire
Spleen Yin deficiency
Spleen-Kidney Yang deficiency
Kidney Yang deficiency
Kidney Yin deficiency
Kidney and Liver Yin deficiency
Kidney Essence deficiency
Lung and Kidney Yin deficiency
Lung Yin deficiency
Yin vacuity Fire effulgence
Qi deficiency
Qi and Blood deficiency

In TOM, insomnia and other sleep disorders are caused by a dysfunction of the Heart. Worrying, thinking, or feeling distressed can weaken Heart and Spleen, leading to Qi and Blood deficiency and failing to nourish the Heart and to house the *shen,* thus causing insomnia. Too much sexual activity weakens the Kidneys, and Kidney Yin deficiency causes Fire, which results in a disbalance of Heart and Kidneys, leading to sleep disorders. Another cause can be a poorly functioning Stomach and Spleen, resulting in Dampness and Pleghm obstruction and in heat followed by Phlegm heat, which disturbs the Heart such that it cannot house the *shen*. Moreover, anger leads to Liver Qi stagnation; this may lead to Liver Fire, which disturbs the *shen,* and it cannot be housed in the Heart; hence, sleep disorders follow. Table 3 (Deng, 1999; Flaws & Lake, 2001; Maciocia, 2005) presents an overview of

the patterns that may be found in patients who are diagnosed with a sleep disorder according to WM.

Table 3.

Patterns that might receive a Western diagnosis of a sleep disorder (Deng, 1999; Flaws & Lake, 2001; Maciocia, 2005).

Liver Blood deficiency transforming vacuity heat
Liver Fire harassing internally (also called internal heat)/upflaring Liver Fire
Liver Qi stagnation
Liver Blood stasis
Liver Yin deficiency (with empty heat)
Empty heat/the rising of Minister-Fire/Empty-Fire
Retained heat (in the diaphragm)
Phlegm Fire/heat harassing (the Mind)
Phlegm by a weakness of the Gallbladder
Heart Fire effulgence/upflaring Heart Fire/Heart-Fire blazing
Heart-Spleen (Blood) deficiency
Heart Yin deficiency
Heart-Gallbladder (Qi) deficiency
Heart-Blood deficiency
Heart-Blood stasis
Heart-Blood heat
Heart & Lung Qi stagnation
Non-interaction or disbalance between the Heart and Kidneys
Food stagnation/disharmony of Stomach Qi
Stomach and Heart Phlegm Fire
Kidney Essence deficiency
Yin deficiency (general)
Qi stagnation (general)
Qi deficiency
Qi and Blood deficiency
Blood stasis (general)

Several sleep-tests, such as the Epworth Sleepiness Scale (Johns, 1991), Munich Parasomnia Screening (MUPS) (Fulda et al., 2008), Multiple Sleep Latency Test (Carskadon et al., 1986), Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989), and Sleep diaries (Carney et al., 2012) have been developed in WM in order to diagnose sleep disorders. In our study, the PSQI (Buysse et al., 1989) was used in order to indicate the presence of possible sleep disorders from a WM perspective. The PSQI is a self-rated questionnaire that assesses sleep disturbances and sleep quality over a 1-month

period. It consists of 19 self-rated questions, and these items are grouped into seven component scores, each weighted equally on a 0-3 scale. The global PSQI score is a summation of these seven component scores, and as a result, the global PSQI score can range from 0 to 21. Five was originally used as the cut-off score (Buysse et al., 1989), meaning that participants who score below five have good sleep quality; however, in recent years, six has become the preferred cutt-off score, in order to be more selective (Hametner et al., 2012). Note that in WM, the PSQI is frequently used as a clinical sleep instrument in schizophrenia (Afonso, Brissos, Cañas, Bobes, & Bernardo-Fernandez, 2014) as well as in depression (Lai et al., 2014) and has been found to have high test-retest reliability and a good validity (Backhaus, Junghanns, Broocks, Riemann, & Hohagen, 2002). In this study, a cut-off score of 6 was used.

3. Results

Table 4.

The TOM diagnosis results with the TOM diagnostic patterns of our total psychiatric sample (n = 60) specified for the patients with (PSQI ≥ 6) and without sleep disorders.

Group with WM Diagnosis of Schizophrenia			
TOM Diagnostic Pattern	**Number of Patients**	**PSQI < 6**	**PSQI ≥ 6**
Phlegm misting the Mind	4	1	3
Phlegm heat harrassing the Mind	4	1	3
Qi & Blood deficieny resulting in Phlegm misting the Mind	4	2	2
Stomach and Heart Phlegm Fire	4	3	1
Qi & Blood deficiency	3	1	2
Heart-Blood (Yin) deficiency	2		2
Liver Fire	2		2
Liver Yin deficiency with Liver Yang rising	2		2
Heart and Kidney Yin deficiency	1	1	
Heart & Stomach Yin deficiency	1	1	
Kidney Essence deficiency with upflaring Liver Fire	1		1
Kidney Yang and Yin deficiency	1		1
Liver Qi stagnation from Liver Blood and Yin deficiency	1	1	
Group with WM Diagnosis of Depression			
TOM Diagnostic Pattern	**Number of patients**	**PSQI <6**	**PSQI ≥ 6**
Qi & Blood deficiency	8	2	6
Kidney Essence deficiency	4	1	3
Heart Yin deficiency	2		2
Blood deficiency	2		2
Kidney Yang deficiency	2		2
Phlegm Fire flaring upwards	2		2
Heart Fire with empty heat	1	1	
Heart and Kidney Yin deficiency with empty heat	1		1
Liver Fire	1		1
Liver & Kidney Yin deficiency with Liver Wind	1		1
Liver Qi stagnation leading to Liver Blood Stasis	1		1
Lung & Spleen Qi deficiency resulting in Phlegm misting the Mind	1	1	
Qi & Blood deficiency resulting in Phlegm misting the Mind	1		1

Table continues

TOM Diagnostic Pattern	Number of patients	PSQI <6	PSQI ≥ 6
Stagnation of Hearth & Lung Qi with accompanying Phlegm	1		1
Stomach Phlegm Fire with Wind Phlegm	1		1
Stomach & Spleen Yin deficiency	1	1	

The 30 patients with schizophrenia showed several main patterns (for a complete overview, see Table 4). The most frequent ones were the following: Phlegm misting the Mind, Phlegm heat harrassing the Mind, Qi & Blood deficiency, and Stomach and Heart Phlegm Fire. In diagnosing these patients, it is important to note that most patients had been ill for a long time (more than five years). They had taken heavy medication for many years, which complicated the process of diagnosis. As Ronan, Harbinson, MacInnes, Lewis, and Robinson described (2010), a tongue diagnosis sometimes displayed symptoms of stagnation and heat whereas pulses were weak. Moreover, patterns tend to change with treatments. Therefore, only the patterns that were present at the first treatment are presented here.

The 30 patients with depression displayed the following main patterns (for a complete overview, see Table 4): Qi & Blood deficiency and Kidney Essence deficiency. Note that, also in the patients with depression, diagnosis was sometimes complicated due to long-standing disease patterns and the use of Western medication over long periods of time.

As can be seen in Table 4, the results of the PSQI (with a cut-off score of six) (Hametner et al., 2012) showed that of the 30 patients with schizophrenia, 19 patients (63.33%) suffered from sleep disorders whereas of the 30 patients with depression, 24 patients (80.00%) suffered from sleep disorders. In addition, the TOM diagnosis results of our total psychiatric sample (n = 60) show the following main TOM diagnostic patterns for the patients with sleep disorders: Qi & Blood deficiency, Kidney Essence deficiency, Phlegm heat harrassing the Mind, and Phlegm misting the Mind.

4. Discussion

In this study, we described the different TOM diagnostic patterns in patients with a Western diagnosis of schizophrenia, depression, or sleep disorders from a literature and a clinical perspective. As the results of our study showed, several main TOM diagnostic patterns for schizophrenia and depression could be observed in the study population (see Table 4). The most frequent TOM diagnostic patterns in schizophrenia were Phlegm misting the Mind, Phlegm heat harrassing the Mind, Qi & Blood deficiency, and Stomach and Heart Phlegm

Fire. The most frequent TOM diagnostic patterns in depression were found to be Qi & Blood deficiency, Heart Yin deficiency, and Kidney Essence deficiency.

Research on acupuncture and depression or schizophrenia is difficult to design, conduct and interpret because of the fact that different patterns can be found within these groups of patients. Some patterns are more severe from a TOM point of view, indicating that acupuncture results may differ between different groups of patients. This finding suggests that the group being treated is very heterogeneous in nature and that the results obtained from any particular group may not be generalizable. To solve this problem, a very large number of patients need to be included, or inclusion criteria need to be very strict. Both points create recruiting problems in clinical practice (Patel, Doku, & Tennakoon, 2003). One more point that needs attention in conducting a clinical research is the possibility of an appreciable age difference between the groups. In this case, the analysis of variance showed that our group with depression was (on average) significantly older (*M age* = 49.59 years; *SD* = 7.60 years) than our group with schizophrenia (*M age* = 42.90 years; *SD* = 10.30 years), $F(1,59) = 7.938$, $p < .01$.

In addition, as expected, the study results of our psychiatric sample showed a high percentage of sleep disorders in both the depression group (>80%) and the schizophrenia group (>63%) (see Table 4). It is well known in WM, that sleep disorders occur in depression (Nutt, Wilson, & Paterson, 2008), but they are often underestimated in schizophrenia (Bosch et al., 2012). From a Western point of view, logically, when patients sleep better, their concentration improves and they feel better. From a TOM point of view, explaining why both psychiatric groups suffer from sleep disorders is logical and easy. Sleep disorders occur when the *Spirit* and *Mind* are not calm, and *Shen* cannot house in the Heart. When these problems are solved, sleep normalizes, and the whole body moves towards equilibrium. Based on the clinical results of our psychiatric sample, we hypothesize that the effects of acupuncture treatment on patients with schizophrenia and those with depression may be partially mediated through improvement in sleep (Bosch, Staudte, Van den Noort, & Lim, 2014; Bosch et al., 2013; Reshef et al., 2013).

However, more international (Lee, Shin, Ronan, & Ernst, 2009) and larger studies on acupuncture and schizophrenia (Rathbone & Xia, 2005) and on acupuncture and depression (Smith, Hay, & MacPherson, 2010) are needed, in order to better understand the effects of acupuncture in these patient groups and to test the hypothesis that there is a mediating role of sleep improvement in the treatment of patients with schizophrenia and depression (Bosch et al., 2013, 2014; Reshef et al., 2013). The sleep hypothesis may explain the positive effects of acupuncture treatment observed in patients with schizophrenia (Bosch & van den Noort, 2008) and in depression (MacPherson et al., 2013); thus, treatment of patients with schizophrenia and depression using acupuncture seems to be a promising option.

In this research, we showed that several main TOM diagnostic patterns can be found in patients with schizophrenia and depression. Acupuncture research on patients with depression or schizophrenia is difficult to design, conduct and interpret; in addition, due to the different TOM diagnostic patterns that are treated within the schizophrenia and

depression groups, results differ. Finally, we showed a high prevalence of sleep disorders in our psychiatric sample, and discussed sleep quality as a treatment objective that may play a crucial role in mediating acupuncture-induced treatment effects (symptom reductions) in patients with schizophrenia and depression.

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Chapter 9

Schizophrenia and depression: A systematic review on the effectiveness and working mechanisms behind acupuncture

Based on:

Bosch, P., Van den Noort, M., Staudte, H., & Lim, S. (2015). Schizophrenia and depression: A systematic review on the effectiveness and working mechanisms behind acupuncture. *Explore: The Journal of Science and Healing, 11*(4), 281–291. doi:10.1016/j.explore.2015.04.004

Abstract

Objective: This systematic review assessed clinical evidence for the use of acupuncture as an add-on treatment in patients with depression and schizophrenia and for its underlying working mechanisms.

Data Sources: Four databases (Medline, Scopus, ERIC, and the Cochrane Library) were searched with a cut-off date of March 31, 2014.

Study Selection: Systematic reviews and meta-analyses of acupuncture treatment for depression and schizophrenia were considered for inclusion. The scarcity of acupuncture research involving schizophrenia led to the inclusion of randomized controlled trials and case studies.

Data Extraction: The primary and secondary aims of this study were to evaluate the effects of acupuncture in treating patients with depression or schizophrenia and the possible working mechanisms underlying acupuncture through a systematic literature review.

Data Synthesis: The overall clinical results on using acupuncture to treat depression are promising, but only limited evidence for its effectiveness in treating schizophrenia was found. Acupuncture improves the quality of life, particularly that of sleep, in psychiatric patients. Brain research has revealed that acupuncture has a modulating and normalizing effect on the limbic-paralimbic-neocortical network (LPNN), including the default mode network. Because the LPNN is related to sleep and emotions, this might explain the improved qualities of life and sleep after acupuncture.

Conclusions: From the evidence found in this study, acupuncture seems to be an effective add-on treatment in patients with depression and, to a lesser degree, in patients with schizophrenia, but large well-designed studies are needed to confirm that evidence.

INTRODUCTION

Depression and schizophrenia are both severe psychiatric disorders. In the world population, the lifetime prevalence of schizophrenia is estimated to be about 1% (Bromet & Fennig, 1999), and in most countries 8% to 12% will suffer from depression at some point (Andrade et al., 2003; Kessler et al., 2003); however, note that the lifetime prevalence of depression varies widely, from 3% in Japan to 17% in the United States (Andrade et al., 2003). In Western medicine, treatment for these patients varies from pharmacological interventions (Kane & Correll, 2010; Kupfer, 2005), psycho-social therapy (Cuijpers et al., 2013; Dickerson & Lehman, 2006; Roder, Mueller, & Schmidt, 2011; Wolf & Hopko, 2008), and electroconvulsive therapy (Wang, Lin, Chiu, & Tseng, 2013), to light therapy for depression (Oldham & Ciraulo, 2014), etc. During the last two decades, the use of complementary and alternative medicine (CAM), including acupuncture (Yeo et al., 2012), as an add-on treatment in Western medicine (Eisenberg et al., 1998) has been on the rise, especially among psychiatric patients (Deligiannidis & Freeman, 2014; Samuels, Gropp, Singer, & Oberbaum, 2008). CAM is particularly used in the treatment of depression (Kessler et al., 2001). It is not surprising that in line with this trend, the number of scientific studies on acupuncture has increased as well (Lu, Dean-Clower, Doherty-Gilman, & Rosenthal, 2008).

Traditional Chinese medicine (TCM) has its own theoretical background in which its mechanisms are explained (Maciocia, 2005). In TCM, the forces of nature are described in terms of yin, yang, qi, and the five phases (Switala, 2008). In cases where these forces are not in harmony, disease occurs (Switala, 2008). TCM offers theories and mechanisms based on these theories that describe how one can return harmony within and between people and between them and the world around them (Switala, 2008). Because these theories are difficult to measure, modern science has been searching for biological mechanisms behind acupuncture (Beissner, Deichmann, Henke, & Bär, 2012) that can be measured, tested, and observed. What do these studies reveal? To which extend does acupuncture appear to be a feasible non-pharmacological clinical intervention in patients with depression and schizophrenia? What might its measurable and observable underlying working mechanisms be? In order to address these questions, the use of acupuncture as an add-on treatment in patients with depression and schizophrenia is reviewed in this paper, and competing theoretical paradigms are discussed.

METHODS

Database and search strategies

Four databases (Medline, Scopus, ERIC, and the Cochrane Library) (Xiong, Liu, Yang, Feng, & Wang, 2014; Zeng, Luo, Xie, Huang, & Cheng, 2014) were searched with a cut-off date of March 31, 2014, and all papers with at least an abstract in English were included (Franconi, Manni, Schröder, Marchetti, & Robinson, 2013). Systematic reviews and meta-analyses on acupuncture treatment for depression and schizophrenia were considered for inclusion.

Because of the scarcity of research on the use of acupuncture to treat schizophrenia, randomized controlled trials (RCTs) and clinical case studies in addition to the systematic reviews and the meta-analyses, were also included in order to illustrate what had been found so far and what would be needed in future research to be able to eventually draw firm conclusions on the effectiveness of acupuncture in treating this group of patients. Only studies that used manual acupuncture were included in order to be able to compare the results; therefore, studies with other modalities, for instance electro-acupuncture (An, Chen, Ren, & Wu, 2014), laser-acupuncture (Glazov, Yelland, & Emery, 2014), or acupressure (Yeh, Morone, & Chien, 2014), were excluded.

Study selection and data extraction

Two authors (P. Bosch and H. Staudte) independently conducted the literature search in the different databases. The study selection and data extraction were also independently performed by two authors (P. Bosch and M. Van den Noort). The extracted data included the authors, the title of study, the journal in which the study had been published, the year of publication, the number of participants, methodological information of the study, the treatment process, the details of the control interventions (if any), and finally, the effects of acupuncture treatment and conclusions. A third party (S. Lim) was contacted in case of disagreement with respect to the study selection and/ or data extraction; in all cases consensus was reached.

Aims

The primary aim of this study was to evaluate the effects of acupuncture treatment for patients with depression or schizophrenia through a systematic review. The secondary aim was to evaluate possible working mechanisms underlying acupuncture, again through a systematic review.

RESULTS

Acupuncture treatment studies on depression

Table 1.

Overview of Systematic Reviews and Meta-Analyses on Acupuncture Treatment in Depression: the Year the Study Was Conducted, the Numbers and Kinds of Studies Included, the Type of Paper, and the Conclusions that Were Drawn

Study	*Year*	*Numbers and kinds of studies included*	*Type of paper/Conclusions*
Jorm, Christensen, Griffiths, & Rodgers	2002	5 Controlled trials	Systematic review: The authors state that acupuncture appears promising in the treatment of depression, but more research is needed.
Smith & Hay	2005	7 RCTs[a]	Systematic review and meta-analysis: The authors conclude that there is lacking evidence for the efficiency of acupuncture in treating depression in comparison with medication, wait list control, or sham acupuncture. Moreover, the qualities of the study designs are poor, and the sample sizes are small.
Leo & Ligot	2007	9 RCTs	Systematic review: The authors conclude that it is too premature to suggest a role for acupuncture in the treatment of depression; the evidence thus far is inconclusive.
Wang et al.	2008	8 RCTs	Meta-analysis: First, this meta-analysis shows that the quality of individual trials is low. Nevertheless, it is concluded that acupuncture is an effective treatment for depression.
Zhang, Chen, Yip, NG, & Wong	2010	207 studies	Systematic review and meta-analysis: Acupuncture therapy is safe and effective in treating major depressive disorders and post-stroke depression, and can be considered as an alternative treatment for the two disorders.
Smith, Hay, & MacPherson	2010	30 studies	Systematic review and meta-analysis: The authors conclude that there is insufficient evidence to use acupuncture treatment for depression. In addition, they state that the results should be taken with caution because there is a high risk of bias in the majority of the trials.
Wu, Yeung, Schnyer, Wang, & Mischoulon	2012	Not reported	Systematic review: The authors conclude that acupuncture is a potential effective monotherapy for depression, and a safe, well-tolerated add-on treatment besides antidepressants. However, more, well-designed studies are needed.

Note. [a] RCT = Randomized controlled trial.

In Table 1, an overview is given for the selected systematic reviews and meta-analyses on the use of acupuncture for treating depression. In total, seven studies fulfilled our inclusion criteria. The overall results on using acupuncture to treat depression seem promising; acupuncture was found to be an effective and safe therapy in treating major depressive disorder (Wang et al., 2008; Zhang et al., 2010). Moreover, it could be used as a safe and well-tolerated add-on treatment besides antidepressants (Wu et al., 2012). However, caution is required (Smith et al., 2010). For instance, Leo and Ligot (2007) draw the conclusion that the effectiveness of acupuncture as a treatment for depression remains unproven and is too premature because more and larger methodologically better-designed Western studies on acupuncture and depression are needed (Wu et al., 2012).

Acupuncture treatment studies on schizophrenia

Table 2.

Overview of Systematic Reviews and Meta-Analyses on Acupuncture Treatment in Schizophrenia: the Year the Study Was Conducted, the Numbers and Kinds of Studies Included, the Type of Paper, and the Conclusions that Were Drawn

Study	*Year*	*Numbers and kinds of studies included*	*Type of paper/Conclusions*
Rathbone & Xia	2005	5 RCTs[a]	Systematic review and meta-analysis: The authors state that there is insufficient evidence to recommend the use of acupuncture to treat patients with schizophrenia based on the studies so far. However, more and better-designed studies on larger sample sizes are needed in order to draw firm conclusions.
Bloch et al.	2010	2 studies	Systematic review and case study reports: The authors report that sleep improved after acupuncture treatment in patients with schizophrenia. In addition, the patients with schizophrenia showed less anxiety and a better mood after acupuncture therapy.

Note. [a] RCT = Randomized controlled trial.

As can be seen in Table 2, in total, two recent systematic reviews and meta-analyses on acupuncture treatment for patients with schizophrenia fulfilled our inclusion criteria (Bloch et al., 2010; Rathbone & Xia, 2005). The reason for this low number is that until now, only a few clinical studies have been conducted involving both acupuncture and schizophrenia. In the study by Bloch and colleagues (2010), sleep was found to have been improved after acupuncture treatment in patients with schizophrenia; moreover, the patients with schizophrenia show less anxiety and an improved mood after acupuncture therapy. In their study, Rathbone and Xia (2005) found limited evidence for the effectiveness of acupuncture

in treating the symptoms of schizophrenia. However, all authors state that more and better-designed studies on larger sample sizes are needed in order to draw firm conclusions (Bloch et al., 2010; Rathbone & Xia, 2005). In addition to the systematic reviews and meta-analyses, only 4 clinical trial studies (see Table 3a), of which 3 are recent Western studies (Bosch et al., 2013; Bouhlel et al. 2011; Reshef et al., 2013; Wu & Bi, 2004; Xu, Su, & Wang, 2010), and 9 are case reports (Bosch, Staudte, Van den Noort, & Lim, 2014; Kane & Di Scipio, 1979; Ronan, Robinson, Harbinson, & Macinnes, 2011; Shi, 1988, 1989; Shi & Tan, 1986; Tani, Suzuki, Takada, Yagyu, & Kinoshita, 2005; Zhang, 1988) (see Table 3b) were found.

Table 3a.

Clinical Trial Studies on Acupuncture Treatment and Schizophrenia: the Year the Study Was Conducted, the Number of Participants, the Kind of Study, and the Conclusions That Can Be Drawn

Study	*Year*	*Number of participants*	*Kind of study/Conclusions*
Xu et al.	2010	*n* = 60	Randomized trial: The authors report that the combined therapy of three-step acupuncture and a small dose of antipsychotics show the same efficacy as a full dose of antipsychotics. However, the initiation time is shorter and there are fewer side effects than with a full-dose antipsychotic treatment.
Bouhlel et al.	2011	*n* = 31	Randomized trial: The scores on the Positive and Negative Syndrome Scale (Kay, Fiszbein, & Opler, 1987), the Scale for the Assessment of Negative Symptoms (Andreasen, 1984a), and the Scale for the Assessment of Positive Symptoms (Andreasen, 1984b) did not change after acupuncture treatment. Thus, no evidence was found for the effectiveness of acupuncture in treating schizophrenic symptoms.
Bosch et al.	2013	*n* = 16	Pilot study: The effectiveness of the acupuncture treatment was found to be higher for schizophrenia than for depression. The authors conclude that acupuncture seems able to improve sleep and may be a suitable and cost-effective add-on treatment for patients with schizophrenia.
Reshef et al.	2013	*n* = 20	Pilot study: The conclusion of the study is that the overall findings suggest that acupuncture has positive effects for treating the symptoms of insomnia and psychopathology in patients with schizophrenia.

So far, the overall results of these clinical trials and case studies have provided limited evidence for the effectiveness of acupuncture in treating the symptoms of schizophrenia (Bouhlel et al. 2011). Nevertheless, in some studies, positive results in the treatment of hallucinations with acupuncture have been reported (Shi, 1988, 1989). In several studies, the hallucinations entirely disappeared (Wu & Bi, 2004; Zhang, 1988) or decreased (Wu & Bi, 2004; Zhang, 1988) whereas in another study, the severity of the hallucination decreased (Bosch et al., 2014), and the patient felt less disturbed (see Table 3b). Here, it is important to note that with respect to the studies conducted on ethnic Chinese patients suffering from hallucinations (Shi, 1988, 1989; Wu & Bi, 2004; Zhang, 1988), the possibility that group expectations might have influenced the positive treatment results for those patients cannot be excluded. However, several studies have indicated that not only the quality of sleep but also the quality of life seemed to be improved in patients with schizophrenia (Bosch et al., 2013, 2014; Reshef et al., 2013) as a result of acupuncture treatment. Tani and colleagues (2005), for instance, found a positive effect when using acupuncture therapy to treat the side effects of long-time drug use in a patient with chronic schizophrenia. Acupuncture had a positive effect when used to treat tardive dystonia, including axial dystonia; the posture of the neck and body improved, and the involuntary movement disappeared completely. Moreover, Xu and colleagues (2010) found that a combined therapy of acupuncture and small doses of antipsychotics showed an efficacy equal to that for therapy using full doses of antipsychotics, but the former was found to have several important advantages: the initiation time was shorter and there were fewer side effects. However, it is important to note that the results of the systematic reviews, as well as comparative and case studies, should be interpreted with caution and that more, larger, and methodologically-sound studies on acupuncture and schizophrenia are needed (Rathbone & Xia, 2005) before any firm conclusions on the (possible) positive effect of acupuncture in treating patients with schizophrenia can be drawn.

Table 3b.

Clinical Case Studies on Acupuncture Treatment and Schizophrenia: the Year the Study Was Conducted, the Number of Participants, and the Conclusions That Can Be Drawn

Study	*Year*	*Number of participants*	*Kind of study/Conclusions*
Kane & Di Scipio	1979	*n* = 3	Case study: Two patients who had had florid schizophrenic symptoms responded positively to acupuncture treatment whereas a third patient, whose symptoms were primarily affective-depressive, showed no significant effect.
Shi & Tan	1986	*n* = 500	Case study: The authors report that in their study, 275 patients with schizophrenia were cured after acupuncture treatment, 84 patients had remarkable improvement, 83 patients had some improvement, and 58

			patients had no improvement.
Shi	1988	*n* = 120	Case study: Therapeutic effects in the treatment of hallucinations with (auricular) acupuncture are reported. The author recommends the use of (auricular) acupuncture in the treatment of hallucinations.
Zhang	1988	*n* = 296	Case study: This study shows that 209 patients with schizophrenia were hallucination free after (scalp) acupuncture treatment, in 56 patients, the hallucinations became indistinct (with stable effects), in 19 patients, there was a partial disappearance or obscurity of one or several kinds of hallucinations (but these effects were unstable), and finally, in 12 patients, the (scalp) acupuncture was ineffective.
Shi	1989	*n* = 120	Case study: The authors report curative effects in treating auditory hallucinations with (auricular) acupuncture therapy. The authors recommend the use of (auricular) acupuncture in the treatment of auditory hallucinations.
Wu & Bi	2004	*n* = 11	Case study: The authors report that in 4 patients with schizophrenia, the auditory hallucinations disappeared, in 5 patients, the number of auditory hallucinations decreased, and in 2 patients, there was no effect. They concluded that a combination of acupuncture and pharmacotherapy in the treatment of auditory hallucinations results in marked therapeutic effects.
Tani et al.	2005	*n* = 1	Case study: The authors report improved symptoms and more stability with regard to the symptoms in a patient with schizophrenia (suffering from severe axial dystonia) after acupuncture treatment. They concluded that acupuncture therapy has a positive effect on tardive dystonia, including axial dystonia.
Ronan et al.	2011	*n* = 11	Case study: The patients diagnosed with schizophrenia seemed to benefit from acupuncture treatment as an add-on treatment (in addition to Western medicine).
Bosch et al.	2014	*n* = 1	Case study: The authors conclude that although larger clinical intervention studies on acupuncture and schizophrenia are needed, their case study results indicate that acupuncture might be beneficial as an add-on treatment for patients with schizophrenia.

Sleep-ameliorating effects in depression and schizophrenia

One underlying mechanism of acupuncture when used to treat patients with schizophrenia and depression that was found seems to be an indirect one, namely, the improvement of sleep (Bloch et al., 2010; Bosch et al., 2013, 2014; Reshef et al., 2013). Bosch and colleagues (2013) found a significant improvement of sleep quality, as measured by using The Pittsburgh Sleep Quality Index (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989), after acupuncture treatment in both patients with depression and patients with schizophrenia (Bosch et al., 2013). Moreover, with objective sleep measures (actigraphs), Reshef and colleagues (2013) found that acupuncture treatment enabled patients with schizophrenia or schizoaffective disorder to fall asleep faster and to sleep better, with less time awake during the night and with reduced activity levels while sleeping. Overall, the sleep of patients with schizophrenia or schizoaffective disorder was found to be better after acupuncture treatment (Reshef et al., 2013). An improvement of sleep was also reported in a recent case study (Bosch et al., 2014); less daytime sleepiness was found after acupuncture treatment in a patient with chronic schizophrenia, as measured with the Epworth Sleepiness Scale (Johns, 1991).

Improvement of emotional processing and mood

Another mechanism of acupuncture when treating patients with schizophrenia and depression that was found in the present systematic review seems to be related to emotions and to mood in particular. For instance, in a meta-analysis by Wang and colleagues (2008), a reduction of depressive symptoms (assessed with the Beck Depression Inventory (Beck, Steer, & Brown, 1996) and the Hamilton Rating Scale for Depression (Hamilton, 1967)) was found after acupuncture therapy in patients with depression. Moreover, Bloch and colleagues (2010) found less anxiety and a better mood after acupuncture therapy in patients with schizophrenia. The same pattern was also found in a recent case study (Bosch et al., 2014), where the patient with schizophrenia was less depressed (measured by using the Beck Depression Inventory (Beck et al., 1996)) after acupuncture treatment.

DISCUSSION

Although more, larger studies involving acupuncture and schizophrenia (Rathbone & Xia, 2005) and acupuncture and depression (Zhang et al., 2010) are needed in order to better understand the effects of acupuncture in these patient groups, the results so far seem to support the idea that one underlying mechanism of acupuncture for treating schizophrenia, as well as in depression, is an indirect one, namely, improved quality of sleep (Bloch et al., 2010; Bosch et al., 2013, 2014; Reshef et al., 2013). A well-known fact is that in patients with depression (Nutt, Wilson, & Paterson, 2008), sleep disorders occur, but in patients with schizophrenia, they are often under-estimated (Bosch et al., 2012). Marked disturbances of sleep have been found in both patients with depression (Ebdlahad et al., 2013; Modell &

Lauer, 2007; Palagini, Baglioni, Ciapparelli, Gemignani, & Riemann, 2013) and patients with schizophrenia (Afonso, Brissos, Cañas, Bobes, & Bernardo-Fernandez, 2014; Cohrs, 2008; Monti & Monti, 2004). They cause huge distress, they can have an extensive impact on the quality of life (Brissos et al., 2013), and they strongly increase the risk of suicide (Nutt et al., 2008). Importantly, psychiatric outpatients reporting sleep disturbance were found to show greater symptom severity and worse adherence/compliance to treatment (Afonso et al., 2014). Prevous sleep research showed a relation between sleep and cognitive functioning; a decrease in sleep had a significantly negative effect on a wide variety of cognitive functions, such as attention, language, reasoning, decision making, learning, and memory (Diekelmann, 2014). Therefore, it seems logical that when patients sleep better as a result of the acupuncture treatment, their cognitive functioning improves; moreover, if their sleep becomes normal, they start to feel better (Wrzus, Wagner, & Riediger, 2014), thereby improving health-related quality of life (Roeser, Eichholz, Schwerdtle, Schlarb, & Kübler, 2012).

A second mechanism of acupuncture when used to treat patients with schizophrenia and depression that was found in the present systematic review seems to be related to emotions and to mood in particular. A reduction of depressive symptoms was found after acupuncture therapy in patients with depression (Wang et al., 2008). Moreover, less anxiety and a better mood were found after acupuncture therapy in patients with schizophrenia (Bloch et al., 2010; Bosch et al., 2014). From previous research, disturbances in the detection of, the response to, and the interpretation of emotions are known to be common in many forms of psychopathologies (Monk, 2008), particularly depression (Gotlib, Krasnoperova, Yue, & Joormann, 2004; Koster, De Raedt, Goeleven, Franck, & Crombez, 2005; Linden, Jackson, Subramanian, Healy, & Linden, 2011; Yang et al., 2011) and in schizophrenia (Anticevic & Corlett, 2012; Anticevic, Repovs, & Barch, 2012; Herbener, Song, Khine, & Sweeney, 2008; Kring & Moran, 2008). These problems are a major cause of persistent functional disability (Herbener et al., 2008). The results of the present systematic review seem to indicate that acupuncture is able to improve mood and emotional processing in patients with depression and schizophrenia; however, it is important to keep in mind that these are preliminary findings based on only the few acupuncture studies so far assessing changes in mood.

These two mechanisms, related to sleep and emotion, seem to be promising in explaining the positive effects of acupuncture treatment that are found, particularly, in patients with depression (MacPherson et al., 2013) and, to a lesser degree, in patients with schizophrenia (Bosch & Van den Noort, 2008) and seem to imply an overall improvement in the quality of life. Although it is too premature to draw any firm conclusions, one interesting hypothesis that needs further investigation is that both acupuncture treatment mechanisms might be based upon and be explained by the “limbic-paralimbic-neocortical network” (LPNN) (Hui, Marina, Liu, Rosen, & Kwong, 2010), as we will discuss in the next session on brain research.

Results of brain research on acupuncture

How do the clinical acupuncture results in patients with depression and schizophrenia that were found in the present systematic review relate to results obtained from brain research? If effects of acupuncture treatment are obvious in patients with depression and schizophrenia, then an interesting follow-up question is whether these clinical effects might be explained with existing brain theories and existing results from brain research involving acupuncture.

Previous neuroscience research found evidence for the existence of a so-called default mode network (DMN) (Buckner, Andrews-Hanna, & Schacter, 2008; Gusnard & Raichle, 2001; Neuner et al., 2014; Raichle et al., 2001; Raichle & Snyder, 2007), which is a system of brain regions that is activated during rest or during passive viewing tasks, but is deactivated when cognitive tasks are performed (Buckner et al., 2008; Gusnard & Raichle, 2001; Raichle et al., 2001). Important components of this network are related to the anterior medial prefrontal area, with a special role for the anterior cingulate gyrus and the precuneus/posterior cingulate cortex posteriorly.

Alterations of the DMN have been found in patients with depression (Andreescu et al., 2013; Wu et al., 2011). In widely-distributed elements of the DMN (e.g., anterior cingulate, lateral parietal cortex, lateral temporal cortex, and ventromedial prefrontal cortex), patients with depression, but not healthy control participants, were found to be unable to reduce activity during an experimental task that included observing and reappraising negative pictures (Sheline et al., 2009). Moreover, significantly greater increases in the activities in other DMN regions, such as the amygdala, hippocampus, and parahippocampus, were found in patients with depression compared to healthy control participants (Sheline et al., 2009). In sum, the pathophysiology of depression is characterized by both stimulus-induced heightened activity and a failure to normally down-regulate activity broadly within the DMN (Sheline et al., 2009).

In addition, there is accumulating evidence of DMN dysfunction in schizophrenia as well (Mingoia et al., 2012; Salgado-Pineda et al., 2011). For instance, a failure of deactivation in the DMN was found in an experiment with facial-emotional items (Salgado-Pineda et al., 2011). Moreover, evidence was found for structural changes in the brain regions of the DMN in patients with schizophrenia (Camchong, MacDonald, Bell, Mueller, & Lim, 2011; Pomarol-Clotet et al., 2010). Finally, it has been suggested that dysfunctional interactions between fronto-parietal control systems and the DMN might explain a psychosis. In other words, psychosis is a network disturbance that leads to disordered thought because it disrupts the fragile balance between the DMN and competing brain systems (Buckner, 2013). In sum, although it is too premature to draw any firm conclusions yet, the general findings on the DMN and schizophrenia seem to be able to explain at least some of the positive and the negative symptoms that are typical for patients with schizophrenia (Mingoia et al., 2012).

Interestingly (see also Figure 1), previous brain imaging research has revealed that the so-called LPNN (Fang et al., 2009; Hui et al., 2005, 2009), consisting of the amygdala (Bai et al., 2009; Chae et al., 2013; Dhond, Yeh, Park, Kettner, & Napadow, 2008), the hypothalamus

(Hui et al., 2010), and the DMN (Bai et al., 2009; Dhond et al., 2008; You et al., 2013), thereby encompassing the limbic system (Hui et al., 2010), is affected in response to acupuncture. More precisely, Hui and colleagues showed that sensations constituting *deqi* (the feeling or sensation that is described in TCM as important for effectivity of the treatment) are related to decreased brain activity in the limbic system and in the DMN whereas sharp pain is related to signal increases (Hui et al., 2010). Note that the hypothalamus is known to play a key role not only in the regulation of sleep and wakefulness (Saper, Chou, & Scammell, 2001), but also in the control of pain (Melzack & Katz, 2013). Within the neuromatrix of pain, a genetic component and a neural-hormonal mechanism of stress, which play equally important roles as neural mechanisms of sensory transmission, are described (Melzack & Katz, 2013). In cases of injury, the neuromatrix of pain states that the body uses several programs of neural, hormonal, and behavior activity in order to turn back to homeostasis (Melzack & Katz, 2013). Previous research showed that acupuncture had a modulating and normalizing effect on the hypothalamus (Hui et al., 2010), which fits the neuromatrix theory of pain (Melzack & Katz, 2013) and seems to support the bodily function of reinstalling homeostasis.

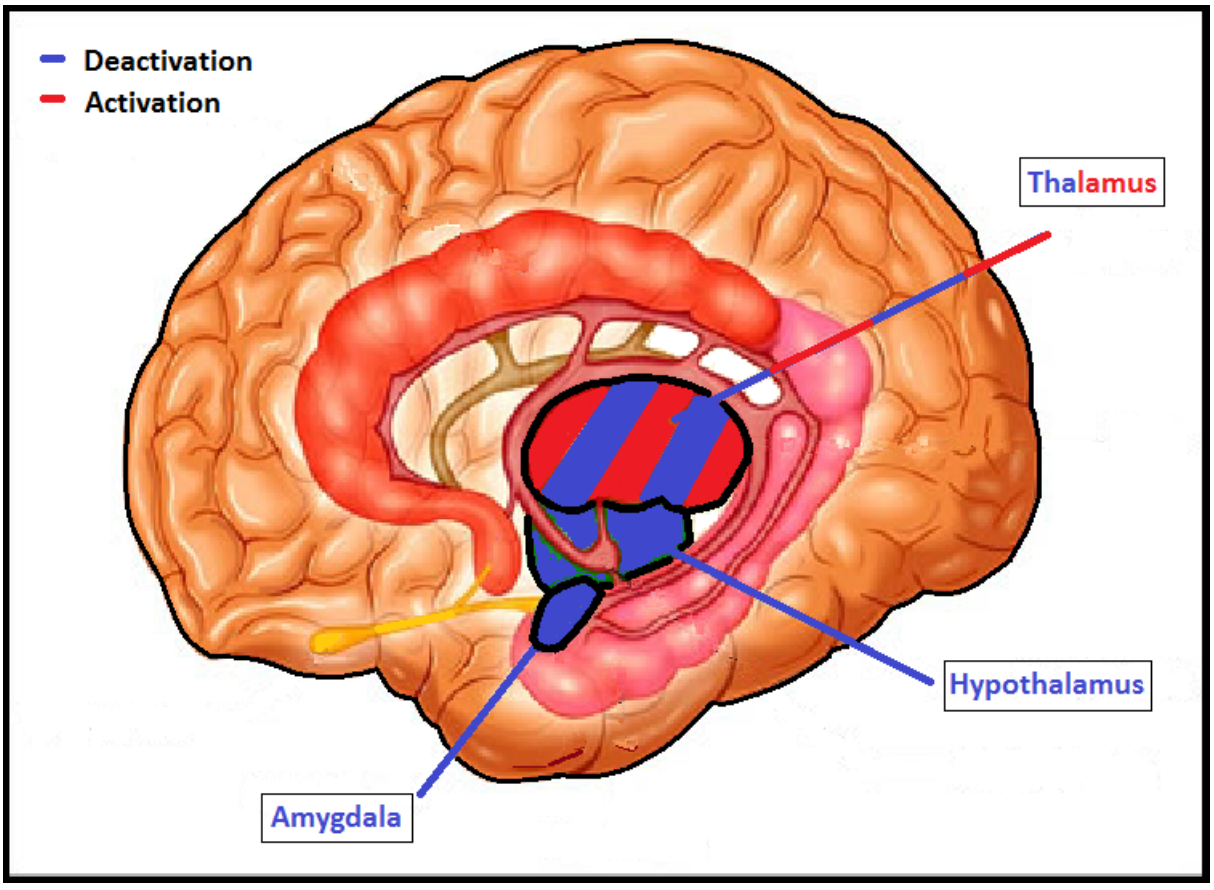

Figure 1. *A brain sketch of the amygdala, hypothalamus, and thalamus, which are part of the LPNN (Hui et al., 2009) and are suggested to play key roles in the acupuncture treatment of patients with schizophrenia and depression. The functionally anti-correlated task-positive areas in response to acupuncture are presented in red whereas the anti-correlated task-negative areas are presented in blue (Hui et al., 2009). Note that, in general, treatment*

resulting in deqi is related to decreased brain activity in the limbic system and in the DMN whereas sharp pain is related to signal increases (Hui et al., 2010).

Another acupuncture treatment mechanism is related to the LPNN (see also Figure 1) (Fang et al., 2009; Hui et al., 2005, 2009, 2010). From previous research, the limbic system is known to play a key role in emotions (Phan, Wager, Taylor, & Liberzon, 2002). If acupuncture, indeed, influences this network, that would explain its influence on emotions. The amygdala, for instance, was found to play a role in encoding positive and negative emotions (Fernando, Murray, & Milton, 2013; Koelsch et al., 2013). Evidence indicates that the limbic system and the structures within the prefrontal cortex show structural and functional alterations in different types of psychopathologies, including schizophrenia and depression (Monk, 2008). It is important to note that not only patients with depression but also many patients with schizophrenia suffer from depressive symptoms (Buckley, Miller, Lehrer, & Castle, 2009). Acupuncture seems to have a modulating and a normalizing effect on the limbic system (Hui et al., 2000), including the amygdala (Bai et al., 2009; Dhond et al., 2008), and a consequence would be that it influences emotions as well.

Limitations

Naturally, the present systematic review has several limitations. The first limitation is the use of only literature published in English. In the present study, all papers with at least an abstract in English were included (Franconi et al., 2013). Although focusing only on literature published in English is not uncommon for review papers on acupuncture (Franconi et al., 2013), this might have narrowed the view. Moreover, only studies that used manual acupuncture were included in our systematic review whereas other modalities, for instance electro-acupuncture (An et al., 2014), laser-acupuncture (Glazov et al., 2014), or acupressure (Yeh et al., 2014), were excluded. There was a methodological reason for this; we wanted to be able to compare the results of different clinical studies, and comparing different modalities would complicate that. However, it is important to note that valid clinical research involving electro-acupuncture, laser-acupuncture, and acupressure for the treatment of depression and schizophrenia has been conducted as well. For instance, recent research with electro-acupuncture showed that it was effective for treating depression and affected personality traits (Wang et al., 2013); moreover, research has indicated that electro-acupuncture might provide improvement in auditory hallucinations and positive symptoms in individuals suffering from schizophrenia (Cheng et al., 2009). Laser acupuncture was found to reduce symptoms of depression that could be measured objectively (Quah-Smith, Smith, Crawford, & Russell, 2013). Not much (recent) research has been conducted with laser acupuncture for treating schizophrenia; however, in an older study, Zhang found that laser acupuncture was as effective as chlorpromazine in the treatment of schizophrenia (Zhang, 1991). Finally, acupressure research showed a significant decrease of depression symptoms (Bergmann et al., 2014), but no significant improvements were found in patients with schizophrenia (Ching, Wu, Chen, & Hsieh, 2012).

In addition, the studies on depression and schizophrenia so far often lack a thorough methodology, and larger groups are needed in order to prove the presumed mechanisms underlying acupuncture treatment and/or to come to alternative explanations. Moreover, the interpretation of the acupuncture findings on depression and schizophrenia so far is challenging because the neurobiology of psychiatric disorders has yet to be fully elucidated (Pilkington, 2013). Moreover, limitations arise from the fact that there are several pitfalls in conducting clinical studies on the effectiveness of acupuncture treatment for patients with depression and, particularly, for patients with schizophrenia. These limitations can explain why so few clinical studies on acupuncture for the treatment of schizophrenia have been conducted and published in Western scientific journals so far.

Another limitation is the absence of a suitable control group or placebo (Wang et al., 2008). Often researchers decide to investigate the “normal” or “real-world” manual individualized acupuncture treatment that a patient would receive if they visited an Oriental medical practitioner (Bosch et al., 2013). However, nonstandardized acupuncture treatment (Chen, 2010), with acupuncture points selected on the basis of traditional practice and theory, makes it hard to draw firm scientific conclusions because the patients, groups, treatments, and studies are hard to compare and data cannot be generalized. On the other hand, the use of a standardized protocol for acupuncture (Cui, Wu, & Luo, 2008) in the treatment of depression or schizophrenia is unheard of in clinical TCM practice and would not be generalizable to routine clinical practice (Schroer & Adamson, 2011). Moreover, evaluating care that is not credible to the patients or the practitioners would result in study findings with low external validity; thus, it would widen the gap between scientific evidence and daily practice, thereby possibly underestimating the potential value or harm of acupuncture intervention (Schroer, Kanaan, MacPherson, & Adamson, 2012).

Another problem for acupuncture research on depression and schizophrenia is that the patients are on different kinds of prescribed drugs and use different doses (Weinbrenner et al., 2009). Particularly, in schizophrenia, this is a huge problem because these patients often use a wide spectrum of medication that can differ from patient to patient and can change over time (Ren et al., 2002). For ethical reasons, controlling the medications is impossible.

When thinking about the different illness patterns from a TCM (theoretical) point of view, every patient is different, and it seems logical that some patterns might be treated more easily than others (which is one reason TCM uses individualized treatment and not a standardized treatment) (Zhang, Sun, Wang, Han, & Wang, 2012). Results might, therefore, be different between these heterogenic patient groups.

Finally, limitations also arise from the fact that many acupuncture studies suffer from small sample sizes (Pilkington, 2010). In daily practice, recruiting large samples of patients with depression and schizophrenia from a clinic is often not possible (Patel, Doku, & Tennakoon, 2003). A solution to this problem might be the use of multicenter studies (Messerer, Porzsolt, Hasford, & Neiss, 1987), which are not uncommon in medicine (Alcolea et al., 2014; López et al., 2004; Reid et al., 2011), but they do have some pitfalls of their own (Messerer et al., 1987); for instance, they create even more heterogeneity (adding a cultural

factor) and add possible treatment differences when it comes to atmosphere, structures of the clinic, etc.

Future research

In future research, it will be important to conduct well-designed acupuncture studies using randomized controlled trials involving patients with depression and schizophrenia in which the subjective experiences of the patients are measured, the impressions of the patients' psychiatrists/therapists are measured, and, at the same time, more objective measurements are implemented in the study design. With respect to the subjective experiences of the patients, one could think of the use of sleep diaries (Hughes et al., 2009), the Pittsburgh Sleep Quality Index (Buysse et al., 1989), the Beck Depression Inventory (Beck et al., 1996), the Hamilton Rating Scale for Depression (Hamilton, 1967), etc.; these are instruments that have been used in acupuncture research before (Bosch et al., 2014; Reshef et al., 2013; Wang et al., 2008) and are filled in by the patients themselves. Moreover, with respect to the instruments that are filled in by the patients' psychiatrists/therapists, one could think of the Positive and Negative Syndrome Scale (Kay et al., 1987), the Scale for the Assessment of Negative Symptoms (Andreasen, 1984a), and the Scale for the Assessment of Positive Symptoms (Andreasen, 1984b) as were, for instance, previously used by Bhoulel and colleagues (2011). The collection of more reliable data with instruments that have been used in acupuncture studies before is particularly important to collect more comparable data on the patients' subjective impressions of the effects of acupuncture treatment and on the psychiatrists/therapists evaluation of its effectiveness. However, in addition, it is important to implement more objective instruments and experimental tasks in future studies in order to reliably measure the effectiveness of and the working mechanisms behind acupuncture therapy. Here, one could think of the use of actigraphs, as was recently used by Reshef and colleagues (2013), the monitoring of sleep with an electroencephalogram (Steiger & Kimura, 2010), and electroencephalogram and functional magnetic resonance imaging studies with experimental tasks on the processing of emotions, for instance, emotion judgment tasks of faces and words (Frühholz, Jellinghaus, & Herrmann, 2011; Lee et al., 2014).

Conclusion

In this systematic literature review, only limited evidence was found for the effectiveness of acupuncture in treating the symptoms of schizophrenia, but the results for depression were more promising, showing that acupuncture was an effective and safe therapy in treating major depressive disorders. Particularly, the qualities of sleep and life (involving emotions) in patients with depression and schizophrenia were found to be improved after acupuncture treatment. Acupuncture seems to be related to the LPNN, including the DMN, which is known to be affected in response to acupuncture and on which acupuncture has been found to have a modulating and normalizing effect. Due to its presumed effect on this network, acupuncture can be expected to improve sleep and to modulate and normalize emotions, which validates future research involving patients with depression and schizophrenia.

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Chapter 10

General Discussion

Discussion

In allopathic medicine, several methods are used in the treatment of schizophrenia and depression. These methods vary from pharmacological interventions (Kane & Correll, 2010; Kupfer, 2005), psycho-social therapy (Cuijpers et al., 2013; Dickerson & Lehman, 2006; Roder, Mueller, & Schmidt, 2011; Wolf & Hopko, 2008), and electroconvulsive therapy (Wang, Lin, Chiu, & Tseng, 2013) for both schizophrenia and depression to light therapy for depression (Lieverse et al., 2011; Oldham & Ciraulo, 2014). Since the mid-nineties of the last century, complementary and alternative medicine (CAM), including acupuncture (Yeo et al., 2012) has increasingly been used as an add-on treatment to Western medicine (Eisenberg et al., 1998), particularly among patients with psychiatric disorders (Deligiannidis & Freeman, 2014; Samuels, Gropp, Singer, & Oberbaum, 2008); in particular, patients with depression often seek CAM treatments (Kessler et al., 2001). Interestingly, along with the increase of add-on treatments that are sought by patients, more and more research has been conducted on acupuncture (Lu, Dean-Clower, Doherty-Gilman, & Rosenthal, 2008). At the beginning of this project, a custom in this research field was to use the abbreviation CAM for complementary and alternative medicine, stressing its difference from Western or allopathic Medicine. Lately, developments and changes in this research field have led to a new name: "integrative medicine". The abbreviation CAM is being used less and less because researchers now tend to stress their goal of striving for an integrative treatment that uses the best of all medicines possible (Rakel, 2012) and to call it as such. The optimal goal for an integrative treatment would be the use of both allopathic medicine and that which was formerly called CAM at one center.

Traditional Chinese medicine (TCM), as part of integrative medicine, has its own theoretical (philosophical) background based on which its mechanisms can be explained (Maciocia, 2005). In TCM, the forces of nature are described in terms of *Yin*, *Yang*, *Qi*, and the *Five Elements* (Switala, 2008). In cases where these forces are not in harmony, disease occurs (Switala, 2008). TCM offers theories and mechanisms based on these forces that describe how one can return harmony within and between people and between people and the world around them (Switala, 2008). Because these theories are difficult to measure objectively by using techniques that are available nowadays, modern science has been searching for biological mechanisms behind acupuncture (Beissner, Deichmann, Henke, & Bär, 2012) that can be measured, tested, and observed. In the case of schizophrenia, the current Ph.D. research is one of the first studies to use acupuncture outside Asia. The research presented in this thesis describes the patient groups at risk: Patients with long-term schizophrenia or depression. Moreover, this project investigated whether acupuncture could be used as an add-on clinical intervention in these psychiatric populations. Because both patient groups

suffer from sleep disorders and a treatment thereof would have a positive influence on their overall well-being (Benson et al., 1991; Benson, 2006, Buysse et al., 2008), sleep disorders are the focus of this project.

First, the sleep behavior and the sleep problems of these long-term psychiatric patients were studied along with their psychopathology and personality. Because acupuncture is thought to be an overall treatment for the patient, in acupuncture, treating only the patients' sleep disorders or only their psychopathologies is not a viable approach. Acupuncture is thought to reestablish equilibrium, which causes the body to move back towards health, thereby minimizing the patients' complaints about their well-being (Gao, 1982). As a result of the suggested improved sleep and decreased psychopathology of the psychiatric patients, improved cognitive functioning would be expected. Therefore, the four main questions in this research were as follows: 1) What possible problems in sleep, psychopathology, and working memory performance can be found in a population of patients with long-term schizophrenia and patients with depression? 2) Does acupuncture improve the patients' sleep? 3) Does acupuncture decrease the patients' psychopathology? 4) Does acupuncture improve the patients' working memory performance?

One modality of acupuncture was used throughout all acupuncture studies in this research: manual acupuncture based upon TCM treatment principles. At every treatment session, a (tongue and pulse) diagnosis was conducted, and acupuncture points were chosen accordingly. Needles were inserted (according to TCM principles when it comes to the depth of insertion) aiming at a *De qi* sensation (an electrical or tingling sensation, also described as "sweet pain", that is thought to be a sign of therapeutic effect) and were left in place for one hour. All patients were treated once a week for 12 weeks. No other interventions were administered, although the patients' usual treatments were continued. Patients were treated in a group and every 15 minutes, two new patients arrived and sat in "rest chairs" that made it possible to sit or lie down as the patient wished. Diagnosis was conducted and the patients were then treated. Due to the group-wise treatment, the two practitioners that were present were always in sight of the patients, and interaction was instantly possible. This group-wise setting was required by the ethics committee, the members of which were concerned about the thought that patients with schizophrenia might respond nervously or even paranoid to needles being inserted and then being left alone for one hour. In this research, patients with schizophrenia and depression were randomly assigned to either a waiting-list group or a treatment group.

Main Findings

In the first study (Chapter 2), the Minnesota Multiphasic Personality Inventory-2 (MMPI-2) (Butcher, Graham, Ben-Porath, Tellegen, Dahlstrom, & Kaemmer, 2001) was used in order to characterize the patients with schizophrenia and depression and to measure the quality of their ability to function. The results showed that patients with schizophrenia differed from

patients with depression on 14 MMPI-2 scales. In general, patients with schizophrenia scored lower on the MMPI-2 scales than the patients with depression, meaning that they experienced a higher quality of their ability to function. In addition, patients with schizophrenia differed from the healthy controls on 10 scales, showing generally higher scores than the healthy control participants, meaning that they experienced a lower quality of their ability to function compared to the healthy control participants. Surprisingly, however, in general, patients with schizophrenia showed mean *UT*-scores < 65, indicating a subjective experience of (near) normal functioning. Furthermore, patients with depression differed from healthy controls on 17 scales, showing higher scores on the MMPI-2 scales and mostly *UT*-scores > 65, indicating impaired functioning. In addition, this first study revealed that demoralization was higher in patients with depression than in patients with schizophrenia and that both psychiatric groups showed higher demoralization than the healthy control group. Based on these results, this study concluded that patients with long-term depression show impaired functioning and high demoralization while patients with long-term schizophrenia surprisingly show near normal functioning and less demoralization (Bosch et al., 2014a). In further studies, the question was whether acupuncture could normalize functioning in these patient groups, keeping in mind that the responses of the group of patients with schizophrenia were nearly normal while the group of patients with depression showed higher scores and were more severely impaired.

In the second study (Chapter 3), the parasomnias and other nocturnal behaviors of the patients with depression and schizophrenia were assessed because this population often complains about sleeping problems. Surprisingly, the results of the parasomnia screening test revealed that, although all patients with depression had experienced nocturnal behaviors, none had had a previous parasomnia diagnosis or had been treated accordingly. In total, 97.6% of the patients in the depression and the schizophrenia groups reported nocturnal behaviors, with the prevalence being highest in the depression group. Overall, these results indicate a need for more clinical awareness of and better treatments for the parasomnias in patients with schizophrenia or with depression. A screening instrument, similar to a parasomnia screening test, is essential in filtering out patients who seem to experience parasomnias. Nevertheless, despite the fact that in our study, patients with depression were to suffer most from parasomnias, patients with schizophrenia and healthy individuals often suffer from parasomnias as well (Bosch et al., 2012). Thus, this study concluded that sleeping disorders occurred very frequently and were an underestimated problem in patients with depression and schizophrenia and even in healthy controls, and that the quality of sleep, in general, needed more attention. As a result a natural question is whether acupuncture can influence sleeping disorders in these patient groups, a subject that was also addressed in this research.

In the pilot study described in Chapter 4, the effects of three months of acupuncture treatment on the sleep of 16 patients with schizophrenia and 16 patients with depression

were evaluated. In addition, eight healthy control participants were included in the study in order to establish reference values (Bosch et al., 2013). Both acupuncture groups were found to show significantly lower scores on the Pittsburgh Sleep Quality Inventory (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) after the treatment period, which was not the case for the waiting-list group. This indicates that sleep quality was improved after twelve weeks of acupuncture treatment. In addition, the effectiveness of the acupuncture intervention was found to be slightly higher in patients with schizophrenia than in patients with depression. This study concluded that acupuncture improved the subjective quality of sleep of patients with chronic depression and schizophrenia and that it might be a suitable and cost-effective add-on treatment for these chronic psychiatric groups (Bosch et al., 2013).

Chapter 5 described a preliminary clinical trial that investigated whether acupuncture had a positive influence on sleep and symptomatology in patients with schizophrenia or depression. In total, one hundred participants were recruited: 40 outpatients with schizophrenia, 40 outpatients with depression, and 20 healthy controls. They all completed a depression inventory, and the positive and negative symptoms of the patients with schizophrenia were evaluated by their psychiatrists. All participants were asked to complete a sleep log (Fischer, Mayer, Peter, Riemann, & Sitter, 2002) for two weeks. For the psychiatric patients, a randomized design with experimental (three months of acupuncture treatment) and control (waiting list) groups was used, after which all measurements were conducted once more. Before treatment, patients with depression were awake longer during the night, needed more time to fall asleep, evaluated their sleep as less relaxed, felt more exhausted, and reported a lower average performance level than healthy controls did. Moreover, patients with depression slept less and felt more exhausted than patients with schizophrenia. Patients with schizophrenia exhibited a lower average performance level compared to only the healthy controls. Acupuncture slightly improved sleep and depressive symptoms in patients with depression, but neither affected sleep nor influenced the positive and the negative symptoms in patients with schizophrenia. These preliminary data suggest that acupuncture can be used in order to reduce the symptoms of sleep disorders and to improve the quality of sleep to some extent in patients with depression, but that acupuncture does not seem to have beneficial effects for patients with schizophrenia (Bosch et al., under review/2015c).

In the study described in Chapter 6, whether acupuncture might be able to improve mood and working memory in patients suffering from depression or schizophrenia was investigated. In total, 50 patients with depression and 50 patients with schizophrenia were randomly divided into an experimental and a waiting-list group. In addition, 25 healthy control participants were enrolled the study. The patients in the experimental groups received twelve weeks of individualized acupuncture treatment, and a pragmatic clinical trial design was used. All patients in the experimental group were tested twice on a mood scale (Becks Depression Inventory-II, BDI-II) (Beck, Steer, & Brown, 1996), a simple working

memory task (digit span task) (Wechsler, 2000), and a complex working memory task (letter-number sequencing task) (Van den Noort, Bosch, & Hugdahl, 2006) both before (T1) and after (T2) acupuncture treatment; the waiting-list group, which did not receive an acupuncture add-on treatment, was also tested twice, but the healthy control participants were only tested at T1. The patients with depression scored worse than the others on the BDI-II, and the patients with schizophrenia scored worse than only the healthy controls. On the digit span test, patients with schizophrenia did not differ from healthy controls, but they scored worse of all on the letter-number sequencing. Acupuncture had a positive effect on the BDI-II for the depression group, but no effects of acupuncture on the digit span and the letter-number sequencing tasks were found. The clinical improvement in depressed patients after acupuncture treatment was not accompanied by any significant changes in their abilities to perform either a simple or a more complex working memory task (Bosch et al., under review/2015d).

Although case studies and qualitative research in general are often seen as “second class science” compared to larger quantitative controlled clinical trials (Shuval et al., 2011), they have their own role in the progress of medical science (Vandenbroucke, 2001) and can give important insights into how a clinical intervention such as acupuncture can affect the daily functioning of a patient. A diagnostic interview described in the case study (Bosch, Staudte, Van den Noort, & Lim, 2014b) (Chapter 7) revealed that the patient experienced improved daily functioning and noticed a change in the experience of the hallucinations after receiving acupuncture treatment. Although the hallucinations did not disappear, the patient, a woman, felt less disturbed by them; moreover, her physical pain as a result of the hallucinations had decreased markedly. The severity of the schizophrenia symptoms was measured by using the Positive and Negative Symptom Scale (PANSS) (Kay, Fiszbein, & Opler, 1987). The positive and the negative symptoms were found not to change immediately, but a decrease in symptoms was found three months after acupuncture treatment. The patient noticed an immediate improvement in sleep. This subjective experience of the patient was further confirmed by the results on the Epworth Sleepiness Scale (Johns, 1991), which is a questionnaire that measures daytime sleepiness. The patient was not able to complete the PSQI (Buysse et al., 1989), which is a (longer) test on sleep quality, beforehand, but was able to do so after the acupuncture treatment period. Finally, a delayed decrease in depression, as measured by the Becks Depression Inventory II (BDI-II) (Beck et al., 1996) was found. The preliminary conclusion is that acupuncture may be beneficial as an add-on treatment tool for patients with schizophrenia (Bosch et al., 2014b). One thing that would not have become clear from the tests that were used, but only became clear after the diagnostic interview, was the subjective experience with hallucinations. The patient felt less bothered by them, but the PANSS after the treatment period did not show this difference instantly due to the fact that it emphasizes the presence of hallucinations over their impact.

In Western medicine, the diagnosis and the outcomes of schizophrenia are often characterized by heterogeneity, meaning that a high degree of variability exists (e.g., Arango, Kirkpatrick, & Buchanan, 2000; McGrath, 2008). Although the DSM-V eliminated all subtypes of the disorder (The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; American Psychiatric Association, 2013), schizophrenia was again proposed to be not one disorder, but many different disorders (Arnedo et al., 2015). In line with this heterogeneity issue (Arnedo et al., 2015), a closer look was taken at the patients with depression and schizophrenia that were included in our studies. The main finding of our study (Chapter 8) was that if a psychiatric group consisting of two subgroups, as was the fact in our sample (patients with depression and schizophrenia) according to Western diagnostic principles is diagnosed on the basis of Traditional Oriental Medicine (TOM) diagnostic patterns, it can be categorized into 28 different groups. This implicates that a very heterogenic group of psychiatric patients is being treated, resulting in many different treatment patterns, causing the research question to change from a clear one: "What effect does acupuncture have on sleep in patients with schizophrenia and on patients with depression?" to a broad and unclear one: "What effect does acupuncture have on sleep in a heterogenic group of patients with several different diagnoses (i.e., different subtypes of schizophrenia/different subgroups of depression)?" Moreover, a high prevalence of sleep disorders was found in patients with both depression and schizophrenia, and those disorders could be explained from the perspective of a TOM diagnostic pattern, resulting in an explanation per pattern, which would explain the different findings in these heterogenic groups. Finally, sleep quality, which may play a crucial role in mediating acupuncture-induced treatment effects in patients with schizophrenia or with depression (Bosch et al., 2015a), as a treatment objective is discussed. This issue will be further discussed later in this thesis.

In the last study (Chapter 9), a literature search was conducted by using four databases, Medline, Scopus, ERIC, and the Cochrane Library, in order to give an overview of the effectiveness and the possible underlying working mechanisms of acupuncture in patients with schizophrenia or with depression. The result showed that the overall clinical results for the use of acupuncture to treat patients with depression could be considered promising (Bosch et al., in press/2015b). On the other hand, only limited evidence for the effectiveness of acupuncture therapy in the treatment of the symptoms of schizophrenia was found (Bosch et al., in press/2015b). However, acupuncture was found to improve the quality of life for both patients with depression and with schizophrenia, and this was particularly so for sleep quality and mood (Bosch et al., in press/2015b). In addition, acupuncture is known to have a modulating and normalizing effect on the "limbic-paralimbic-neocortical network" (LPNN) (Hui et al., 2009), including the default mode network (DMN) (Dhond, Yeh, Park, Kettner, & Napadow, 2008). Because the LPNN is known to behave differently in patients with depression (Sheline et al., 2009) and with schizophrenia (Buckner, Andrews-Hanna, & Schacter, 2008) and because the activation of this brain network is related to sleep as well as emotions, this might explain why quality of life (defined as "The degree to which a person

enjoys the important possibilities of his or her life" and involving the experience of satisfaction and enjoyment, thereby encompassing emotions more generally) (Laliberte-Rudman, Hoffman, Scott, & Renwick, 2004) and the quality of sleep improve after the normalizing effect of acupuncture has modulated these areas (Bosch et al., in press/2015b). Finally, the conclusion of the paper is that acupuncture can be used as an add-on treatment in patients with depression, and to a lesser degree in patients with schizophrenia, but larger, well-designed, future studies are needed to confirm this (Bosch et al., in press/2015b).

Answers to the Research Questions

The four main research questions in this study were as follows: 1) What possible problems in sleep, psychopathology, and working memory performance can be found in a population of patients with long-term schizophrenia and patients with long-term depression? 2) Does acupuncture improve the patients' sleep? 3) Does acupuncture decrease the patients' psychopathology? 4) Does acupuncture improve the patients' working memory performance?

In order to answer the first research question, a population of patients with long-term schizophrenia and patients with long-term depression was tested in order to establish possible problems in sleep, psychopathology, and working memory performance. This research demonstrated that not only patients with depression, but also patients with schizophrenia and healthy individuals, suffer from parasomnias. These sleeping disorders occur very frequently and are an underestimated problem that requires more research and more attention during treatment (Bosch et al., 2012). Moreover, the patients with depression were found to sleep for shorter periods of time and to feel more exhausted than patients with schizophrenia, and compared to the healthy controls, they were awake longer during the night, needed more time to fall asleep, indicated their sleep as being less relaxed, felt more exhausted, and had a lower average performance level whereas the patients with schizophrenia exhibited only a lower average performance level compared to healthy controls. Moreover, patients with long-term depression showed impaired functioning, higher levels of psychopathology, and high demoralization while patients with long-term schizophrenia surprisingly showed near-normal functioning and psychopathology levels and less demoralization (Bosch et al., 2014a). As for working memory performance, the patients with depression scored worse than the healthy controls on working memory tasks while the patients with schizophrenia only scored worse than the healthy controls and the patients with depression on a complex working memory task. Overall, patients with long-term depression scored worse than the patients with long-term schizophrenia, who showed some elevations in their personality profile and showed some psychopathology, but this was much less than what had been expected beforehand (Bosch et al., 2014a). The differences between the schizophrenia and the healthy control groups on many subscales of the MMPI-2 were not that large, and based upon research that was conducted beforehand (on both chronic as well as acute cases), this was unexpected. A possible explanation could be that

patients had been ill for a long time and had started to see their chronic illness more and more as “normal”. On the other hand, patients with depression, who had also been ill for a long time, report more problems than patients with schizophrenia when it comes to psychopathology and personality. Another possibility may be that patients with schizophrenia can be stabilized easier or more effectively by medication than patients with depression? In order to answer the other three questions, further studies need to focus on acupuncture, which supposedly has a normalizing function. Although some colleagues and the local ethics committee doubted the possibility of using acupuncture in a psychiatric clinic, the studies reported in this Ph.D. thesis demonstrate that acupuncture can safely be used in the treatment of patients with schizophrenia and with depression. None of the patients with schizophrenia reported suffering from hallucinations as a result of the needling during the project or reported adverse effects. In contrast, the patients with schizophrenia were and remained highly motivated to participate during the treatment period of 12 weeks. Therefore, the conclusion can be drawn that treating patients with schizophrenia by using acupuncture in addition to their regular Western treatment is clinically possible and safe, as long as strict guidelines are followed and the patients with schizophrenia are monitored carefully. One should note that treatment was given group-wise; patients were not left alone with needles inserted.

Acupuncture for Sleep Improvement

In the introduction of the present Ph.D. thesis, a possible underlying working mechanism of acupuncture in the treatment of patients with depression and with schizophrenia was suggested. It was thought to be an indirect one, namely, the improvement of sleep (Bloch et al., 2010; Bosch et al., 2013; Reshef et al., 2013; Bosch et al., 2014b). In contrast to the subjective questionnaires used in the present Ph.D. research, Reshef and colleagues (2013) also used objective indicators of movement of the limbs (actigraphs) in their acupuncture study on patients with schizophrenia and found that acupuncture treatment enabled patients with schizophrenia or schizoaffective disorder to fall asleep faster and to sleep better, with less time awake during the night and with reduced activity levels while sleeping. Overall, the sleep of patients with schizophrenia or schizoaffective disorder was found to be improved after acupuncture treatment (Reshef et al., 2013).

As to sleep, which was the second research question, in Chapter 4, a pilot study was reported in which the effectiveness of acupuncture was found to be higher in patients with schizophrenia than in patients with depression. In this study, the PSQI was used, resulting in a total score, for which there is a cut-off. In the other studies within this Ph.D. thesis, hardly any results were found within the group with schizophrenia, specifically not on sleep (see Chapter 5). This incongruence raises questions as to how this difference came about. However, the results might be due to the method used. The results in Chapter 5 are based on a sleep log that was completed by the patients every day for two weeks, and the measurement in Chapter 4 was the PSQI, a questionnaire that was completed by the

patients in about ten minutes and evaluated their sleep during the previous two weeks. Due to the form of the questions that were asked, one instrument might be more sensitive to problems and changes within a population. Another possibility may be found in the fact that the seriousness of the illnesses, as in the deviation from the norm, was larger for one measurement (sleep log) than for the other (PSQI) before treatment. In Chapter 5, the patients with schizophrenia reported that they already slept nearly 8 hours per night, with a sleep latency of about 26.17 minutes and a time awake during the night of 11 minutes, and their sleep was found to be more relaxing than that of the control group. Based on these data, acupuncture logically appears to have less effect, and the scores are mostly comparable to those of the healthy norm group. On the other hand, in Chapter 4, the total PSQI score of the patient group with schizophrenia that was to receive acupuncture showed disturbed sleep (larger than 5 or 6, depending on the chosen cut-off score, with a mean score of 8.50). These patients might judge their sleep as worse than normal even though their actual sleep performance seemed comparable to that of the healthy controls. Nevertheless, more deviation would mean more work for acupuncture, which is supposed to help the body strive for equilibrium and return to a “normal” state.

In sum, the present Ph.D. thesis did not find proof against the possible working mechanism of acupuncture via sleep, but was not able to find solid proof either. Therefore, more research with larger, well-developed, clinical studies on the possible working mechanism of acupuncture via sleep is needed (Bosch et al., in press/2015b). As to the effects of acupuncture on sleep in patients with schizophrenia, acupuncture did not seem to have a statistically significant effect on their sleep performance, even though they individually seemed to feel that their sleep had improved. As to sleep in patients with depression, their sleep seemed to improve slightly (see also Chapter 5); however, their sleep seemed to be improved less than the sleep in the patients with schizophrenia. These results need to be interpreted with caution due to the limitations that will be discussed later.

Acupuncture on psychopathology

As for the scores on the BDI-II and the PANSS, in the patients with schizophrenia, no results for acupuncture could be found on the BDI-II (see Chapters 5 and 6). Only in the case study could a delayed improvement be found (see Chapter 7), and in the literature review, some positive results were found (see Chapter 9). No acupuncture results were found on the PANSS (see Chapters 5, 6, and 7) for the patients with schizophrenia. When it comes to the group with depression, results indicate a positive effect for acupuncture (see Chapters 5, 6, and 9) on the BDI-II, which would mean that psychopathology decreased in that group as a result of acupuncture.

All in all, the results that were found on psychopathology in patients with long-term schizophrenia within this Ph.D. thesis indicate that acupuncture does not do much for these patients. In patients with depression, the above-mentioned studies indicate a normalizing

effect for acupuncture on their depressive symptoms, which is regarded as the main finding of this Ph.D. thesis. However, these studies have several limitations, which will be discussed below.

Acupuncture for Working Memory

In Chapter 6, patients with depression were found to score worse than the others on the BDI-II, and the patients with schizophrenia were found to score worse than the healthy controls. On the more simple working memory task (digit span), patients with schizophrenia did not differ from the healthy controls whereas they scored worse of all on the more difficult working memory task (letter-number sequencing). Patients with depression scored worse on the digit span task than the healthy controls, but their scores were comparable to those of the patients with schizophrenia. Moreover, patients with depression scored higher than the patients with schizophrenia on the letter-number sequencing, but their scores were comparable to those of the healthy controls. No indications were found for a possible role of acupuncture in enhancing working memory performance. In this study as well, patients with schizophrenia showed near-normal functioning on the simple working memory test; thus, no or very little improvement could be achieved by using acupuncture. On the complex working memory test, the scores in both groups were worse than the scores in the healthy control group, but no statistically significant effect was found here either. The lack of positive results on working memory in the depressed group, together with the positive effects on mood and sleep, questions the often assumed relationship between mood and sleep on the one side, and cognition, in this case working memory, on the other.

Limitations

The studies presented in the present Ph.D. thesis have several limitations. One limitation is that the samples of patients with depression and with schizophrenia were rather small, a common problem in clinical acupuncture research (Pilkington, 2010). A multicenter study (e.g., Alcolea et al., 2014; López et al., 2004; Messerer, Porzsolt, Hasford, & Neiss, 1987; Reid et al., 2011) is imperative not only to increase the sample size, but also to exclude the effects due to the practitioners and the atmosphere (Messerer et al., 1987).

Another limitation is the absence of a suitable control group or placebo treatment group (Wang et al., 2008). Placebo needles have some disadvantages of their own; for instance, they are rather costly, which made it impossible to include them in the present research. However, three placebo needle devices are available and research is ongoing in this area, constantly improving the needles and making them more suitable for research purposes (Park, White, Lee, & Ernst, 1999; Streitberger & Kleinhenz, 1998; To & Alexander, 2015).

On the one hand, the advantage of the waiting-list approach combined with a group that receives treatment according to the immediate diagnosis at each treatment is that one is able to draw conclusions based on clinical data that are nearest to those of “real-life”

acupuncture. On the other hand, the disadvantage of this approach is that the non-standardized acupuncture treatment (Chen, 2010) of patients with depression and with schizophrenia makes it hard to compare patients, groups, and treatments. However, one must keep in mind that the use of a standardized protocol (the same for every patient) for acupuncture (Cui, Wu, & Luo, 2008) in the treatment of patients with depression or schizophrenia (or any other disorder for that matter) is not accepted in clinical TCM practice (Schroer & Adamson, 2011; Schroer, Kanaan, MacPherson, & Adamson, 2012). The individualized treatment is being dynamically adjusted to the changing needs of the patient; therefore a one-size-fits-all approach cannot be used.

One methodological point that was raised in this Ph.D. thesis is the "fruit basket" problem, meaning that TOM diagnostic patterns might be used in acupuncture research aiming to re-order patient groups and to create groups that might be more comparable than the groups based upon Western diagnoses (using the DSM-V) that have been used so far (e.g., depression versus schizophrenia). Possible hidden effects of acupuncture might be found with a proper re-ordering based on an appropriate Eastern Medicine system instead of the Western Medicine system.

Further limitations are that patients used medication during the entire time and the group with schizophrenia used more medication than the group with depression. From a TCM perspective, medication sometimes does not work towards equilibrium and may even cause more or different problems than the initial reasons for taking it; i.e., it might work against acupuncture (Yang, 2008). As a result, 12 weeks of acupuncture might not be sufficient to make a strong difference, especially because in most cases, the medication and the illness had been present for a long time; according to TCM, this would increase the treatment period needed to achieve results (e.g., Cheng, 1987; Flaws & Lake, 2003). Note that the patients with schizophrenia had been ill longer, thereby possibly explaining their smaller effects. Moreover, medication may mediate acupuncture effects in various ways. For instance, tricyclic antidepressants are thought to be able to suppress *Qi* and *Yang* and to cause *stagnation* and with that an accumulation of *dampness* and *water*, eventually even causing *Phlegm* (Yang, 2008). Moreover, several neuroleptic drugs have been reported to cause *Yin Vacuity* with *Internal Heat* (Flaws & Lake, 2003), which is the opposite of what acupuncture is trying to achieve. In TCM, the current clinical picture of the state of the client is called a diagnostic pattern. The clinical effect of the state resulting from tricyclic antidepressants that was just described would be weight gain, tiredness, and a feeling of heaviness in the body (Yang, 2008). Although anti-depressive medications have the goal of treating depression, they may cause some other imbalance in the body, which is something that acupuncture will try to alleviate. Every medication has its own effects on the body, so one medication might cause more problems in the system than another, which might also differ from patient to patient, depending on the situation and the level of disturbance.

Further limitations were that the study design did not work well due to the large drop-out of patients in the waiting-list groups, the patients with schizophrenia showed near-normal functioning on some of the tests so that not much could be normalized, and the fact that some tests (like the PANSS) did not seem to be sensitive enough. Due to these limitations, the results in this Ph.D. thesis should be interpreted with caution and regarded as preliminary results.

Future Research

TCM/TOM Diagnostic Patterns and Western Diagnosis: The Fruit Basket Problem

Using larger groups would help in solving or demonstrating the previously discussed "fruit basket problem" (Bosch et al., 2015a) because within larger groups of patients, the subgroups according to TCM/TOM patterns will be larger as well, so sufficient statistical power will be retained to answer the question whether patients with a similar pattern respond similarly to acupuncture. Moreover, larger homogenous groups might allow the question whether these patterns can predict whether patients respond well to acupuncture to be answered. In TCM/TOM, as was previously described in Chapter 8, several main TOM diagnostic patterns can be found in patients with schizophrenia and patients with depression (Bosch et al., 2015a). Different TCM/TOM researchers may organize their patients according to Western diagnoses, resulting in several different TOM diagnostic patterns within the groups (TOM diagnostic patterns are the conclusions that a practitioner draws after extensive TOM diagnosis on the Tongue and the Pulse by listening and smelling, observing, and touching). Thus, in TOM, the groups may differ markedly, even though their Western diagnoses are comparable, thereby causing the research results on acupuncture to be less comparable and generalizable than they otherwise would have been if this information regarding their TCM/TOM diagnostic patterns had been added to the research articles. Nearly no TCM or TOM articles so far have stated the diagnostic patterns that they included. In future research, a table should be added stating all patterns within the sample, and groups that are homogeneous according to TCM/TOM patterns should be evaluated and compared.

A second problem is the question how these patterns came about. Little research has been conducted on the inter-rater reliability of TCM practitioners when it comes to TCM diagnostics. One study on three practitioners with extensive experience showed that agreement on TCM diagnosis was low (Zhang et al., 2004). If this problem is to be solved, a pulse measurement machine (Chen, Chang, Jwo, Hsu, & Tsao, 2015) and a standardized tongue measurement (Bosch, Van den Noort, Staudte, Yeo, & Lim, to be submitted) should be used, and those results, in addition to the TCM patterns that were found, should be reported. In our studies, we reported the points that were used, which is also something that will enhance research in the acupuncture field by making clearer what was actually done during the experiment. Moreover, if medication is used, a clear overview should be

presented of the type and the dose of the medication, which might be used to establish homogenous large groups.

Moreover, how can scientific conclusions be drawn about the usefulness of acupuncture when TCM and Western medicine differ in how the depression and the schizophrenia groups should be clinically described? Note that even in Western medicine lively debate on how to best deal with the heterogeneity of the schizophrenia group is ongoing (e.g., Arango et al., 2000; McGrath, 2008); should this patient group be described as one clinical group or should it be further divided into subgroups of schizophrenia (Arnedo et al., 2015)? Homogenous groups need to be created, and research must be conducted accordingly.

One of the problems within the present Ph.D. project was the number of participants that were lost in the waiting-list groups. One statistical method that might be a promising solution to (at least a part of) this problem might be the use of a multilevel analysis (e.g., Jongsma et al., 2011; Pfeffermann, Skinner, Holmes, Goldstein, & Rasbash, 1998; Snijders, 2003; Snijders & Bosker, 1999). When using repeated measures within individuals, the repeated measures constitute the lower (first) and the individuals the higher (second) levels. Time can be used as a factor of change. Especially for non-balanced longitudinal data structures, such as are often seen in acupuncture research in which the numbers and the times of observations differ between individuals (possibly due to dropout), multilevel modeling may be the most suitable method and seems to be a promising new direction for analyzing clinical acupuncture research data.

The instruments that have been used in the present Ph.D. project have the disadvantage that they are only able to collect subjective sleep quality data. In future research, the use of actiwatches (van de Wouw, Evenhuis, & Echteld, 2013) seems to be an interesting next step because actiwatches give the opportunity to collect objective sleep quality data (van de Wouw et al., 2013) for the patients with depression and with schizophrenia without having to have them admitted to a sleep laboratory. In addition, the use of melatonin measures (Benloucif et al., 2008) seem to be promising because melatonin levels are known to be disturbed in patients suffering from sleep disorders (U.S. Department of Health and Human Services, 2004). Thus, comparing the melatonin levels of patients with depression to those of patients with schizophrenia, who were found to suffer markedly from sleep disorders in the present Ph.D. thesis, before and after acupuncture treatment in order to get an objective (biological) measure of possible acupuncture effects would be interesting. Moreover, placebo needles (Park et al., 1999; Streitberger & Kleinhenz, 1998; To & Alexander, 2015) might be used in order to establish a more suitable control group.

Finally, conducting fMRI research on acupuncture intervention in patients with depression and with schizophrenia would be highly interesting. This is particularly important in order to test the modulating and the normalizing effects of acupuncture on the LPNN, including the

default mode network (DMN) (see Figure 1). Alternatively, one could also make use of skin conductance measures (Park & Kim, 2011), event-related potentials (ERP) (Liddell, Williams, Rathjen, Shevrin, & Gordon, 2004), fMRI (Mothersill et al., 2014), combined skin conductance/fMRI (Williams et al., 2007), or combined EEG/fMRI recordings (Trautmann-Lengsfeld, Domínguez-Borràs, Escera, Herrmann, & Fehr, 2013) in order to test the previously-discussed LPNN hypothesis (Bosch et al., in press/2015b).

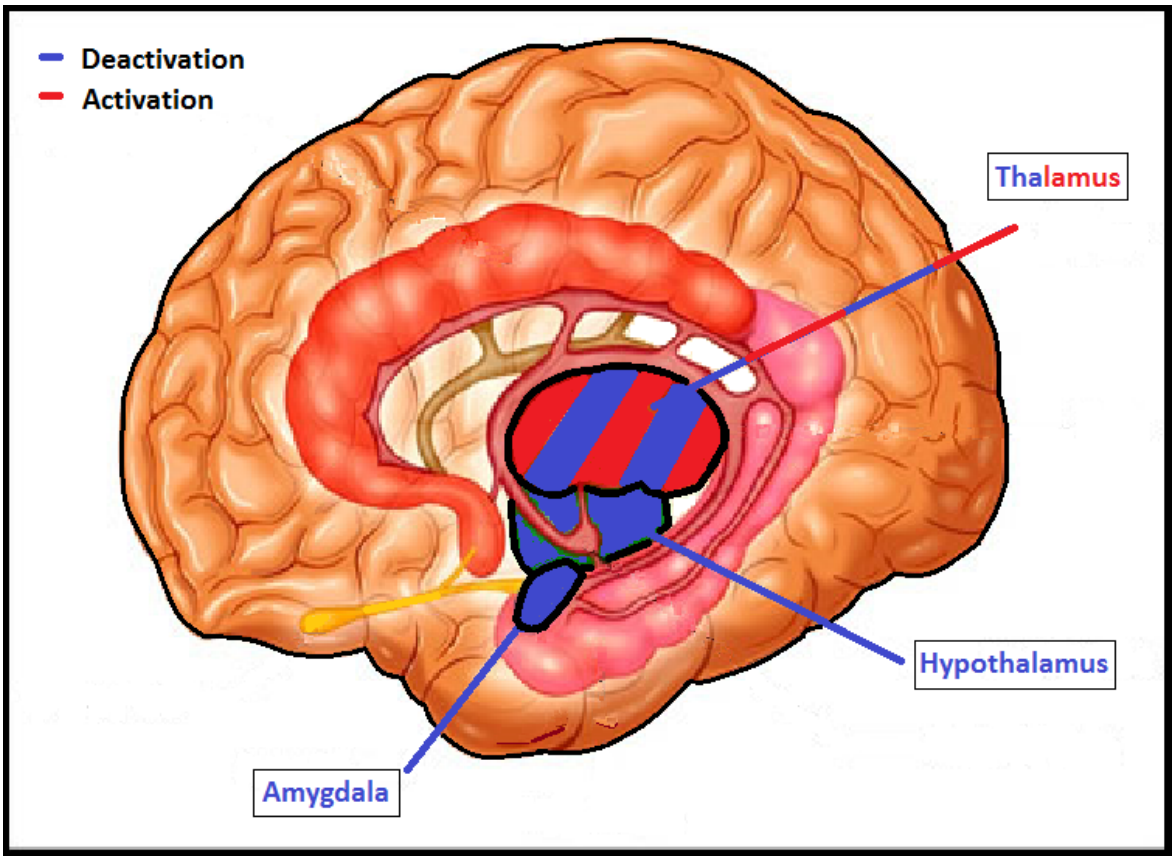

Figure 1. A brain sketch of the amygdala, hypothalamus, and thalamus, which are part of the LPNN (Hui et al., 2009) and are suggested to play key roles in the acupuncture treatment of patients with schizophrenia and depression (Bosch et al., in press/2015b). The functionally anti-correlated task-positive areas in response to acupuncture are presented in red whereas the anti-correlated task-negative areas are presented in blue (Hui et al., 2009). Note that, in general, treatment resulting in *De qi* is related to decreased brain activity in the limbic system and in the DMN whereas sharp pain is related to signal increases (Hui, Marina, Liu, Rosen, & Kwong, 2010).

Conclusions

Stronger indications were found for acupuncture's effectiveness in patients with long-term depression than in those with long-term schizophrenia, for whom only the PSQI positive effects of acupuncture on sleep were established. In patients with depression, acupuncture helped to improve their mood, which might have been due to its positive effect via sleep.

For future research, objective (Western) measuring techniques, such as polysomnography, actiwatches, and brain imaging studies, are necessary for progress in the field. These techniques should be used in multicenter studies in which randomized (possibly partly blinded by using placebo needles) trials are used with sufficient numbers of patients to be able to divide them into groups according to TCM diagnostics. Western measuring techniques combined with Eastern diagnostics techniques with large groups of patients should reveal the real effects of acupuncture.

Building a bridge between East and West in order to come to a true integrative treatment that helps patients more than Eastern or Western treatment alone can do seems to be a goal that is worth working towards. Despite the pitfalls and strong criticisms that belong to a road less travelled, these patients are worth every step it takes.

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English Summary

During the last two decades, the use of acupuncture as an alternative additional treatment in Western medicine has been on the rise, especially among practitioners treating psychiatric patients. Acupuncture is particularly used as a therapy in patients with depression, and recently clinicians have also started to use it to treat patients with schizophrenia. However, solid scientific research on the effectiveness of acupuncture in the treatment of patients with depression and with schizophrenia is scarce, and in particular, research on the efficacy of acupuncture in the treatment of patients with long-term psychiatric disorders is completely missing. The research question of the present PhD thesis is, therefore, whether acupuncture can be successfully used as an add-on in the treatment of patients with long-term depression and of patients with long-term schizophrenia. However, before testing the possible efficacy of a new treatment, good insight into the patient groups under investigation, patients with schizophrenia and patients with depression, is important. Many patients suffer from depression or schizophrenia for a long time, and these disorders can be seen as chronic when they last at least five years. An overview of the diagnostic criteria used for patients with schizophrenia and for patients with depression is given in **Chapter 1**. Within the chronic schizophrenia group, as well as the chronic depression group, patients often differ in their signs and symptoms. When it comes to schizophrenia, different outcomes were found in several studies, and those outcomes might be explained by the heterogeneity of the patient group in focus; the same problem of clinical heterogeneity was found for patients with depression. Factors of chronicity might be responsible for different outcomes between studies because patients might function and feel different in the first five years after having been diagnosed with a psychiatric disorder than in the years that follow, and in many studies, the years of illness are not reported, and mixed groups are used. Moreover, ample evidence exists for a correlation between psychiatric disorders and various sleep disorders, which is another aspect that needs consideration as it can partially explain why heterogeneous clinical results are found within the schizophrenia group and within the depression group. This is further supported by the fact that previous research has shown that when sleep disorders are untreated, the risk of developing psychiatric disorders increases. The aim of the current thesis is to investigate whether acupuncture can be used as an add-on clinical intervention in the treatment of patients suffering from chronic schizophrenia or depression and sleep disorders. In order to do so, the problems behind heterogeneous groups are taken into account, and the patient groups are studied more into detail when it comes to psychopathology and sleep.

In **Chapter 2**, a study is presented that investigated whether the long-term illness of the patients with depression or with schizophrenia might itself influence the way these patients present their psychopathology and personality on the MMPI-2 (Minnesota Multiphasic Personality Inventory-2), a personality inventory. Moreover, the question was whether demoralization, which can be described as a response that may follow chronification of the

disorder, affects the scales of the personality inventory. The patients with long-term schizophrenia, the patients with long-term depression, and the healthy participants completed the MMPI-2 and were compared on the Clinical Scales and on the Restructured Clinical Scales. Demoralization was higher in patients with depression than in patients with schizophrenia, and both psychiatric groups differed from the healthy control group. It is concluded that patients with long-term depression show impaired functioning and high demoralization while patients with long-term schizophrenia, surprisingly, show near normal functioning and less demoralization. The latter may have serious consequences for whether and how much improvement can be achieved with an add-on therapy in the chronic schizophrenia group. Moreover, this finding gives rise to several questions when it comes to the MMPI-2 because a severely disturbed patient group that scores (nearly) normal is something that clearly warrants further research.

In **Chapter 3**, another aspect is considered, namely, the question whether our psychiatric patient groups, indeed, suffer from sleep disorders as is often reported in the literature; moreover, when this is the case, from what kinds of sleep disorders do they suffer? The subjective experience with parasomnias and other nocturnal behaviors in patients with depression and with schizophrenia is investigated by using a parasomnia screening test. In total, 21 parasomnias and other nocturnal behaviors were assessed. Although all patients with depression had experienced nocturnal behaviors, none were found to have had a previous parasomnia diagnosis or to have been treated accordingly. Of all participants, 97.6% had experienced nocturnal behaviors. The prevalence of nocturnal behaviors was highest in patients with depression, indicating a need for more clinical awareness and thereby better future treatments for better outcomes. A screening instrument like a parasomnia screening test is essential in filtering patients who seem to experience parasomnias. Nevertheless, the fact that patients with schizophrenia, as well as healthy persons, also have parasomnias must be kept in mind. In sum, this study clearly showed that both patient groups suffer from sleep disorders, making this an important issue that needs to be taken into account when developing and testing new treatments for patients with chronic schizophrenia and with chronic depression.

After gaining insights into our chronic psychiatric patient groups, we investigated one of the main questions of this thesis. Acupuncture, which is a Traditional Chinese Medicine (TCM) technique, is used as an add-on (in addition to the standard allopathic medicine) treatment for patients suffering from chronic schizophrenia and from chronic depression. **Chapter 4** describes a preliminary clinical trial, in which the question of whether acupuncture has a positive influence on sleep in patients with schizophrenia or with depression was investigated. As was discussed in **Chapter 3**, these patient groups suffer from sleep disorders. All participants with psychiatric disorders were asked to complete the Pittsburgh Sleep Quality Inventory before and after the acupuncture treatment that had been individualized based on traditional Chinese medicine principles; participants on the waiting

list also completed the Inventory. Both acupuncture groups showed significant lower scores on the sleep inventory, which was not the case for the participants on the waiting list. Moreover, the effectiveness of the acupuncture treatment was found to be higher in the patients with schizophrenia than in the patients with depression. From this study, acupuncture seemed to improve sleep in patients with long-lasting psychiatric problems and may be a suitable and cost-effective add-on (in addition to the standard allopathic) treatment for this group, particularly if conducted group-wise.

In **Chapter 5,** the possible clinical effect of acupuncture on sleep is further investigated. The study again describes a preliminary clinical trial investigating whether acupuncture has a positive influence on sleep and symptomatology in patients with schizophrenia or with depression. This time, all participants were asked to complete a sleep log for two weeks. In addition, the psychiatric patients filled in a depression scale, and the psychiatrists filled in a scale on the positive and the negative symptoms of the patients with schizophrenia. Then, the patients with schizophrenia and the patients with depression were randomly divided into an acupuncture group (three months, once a week) and a control group, and after three months, all tests were repeated. Patients with depression are found to sleep for less time and to feel more exhausted compared to patients with schizophrenia; moreover, compared to the healthy controls, patients with depression are awake more during the night, need more time to fall asleep, have sleep that is seen as being less relaxed, feel more exhausted, and have a lower average performance level whereas the patients with schizophrenia solely report a lower average performance level compared to healthy controls. Acupuncture slightly improved sleep and depressive symptoms in patients with depression, but did not affect sleep nor influence positive or negative symptoms in patients with schizophrenia. These data suggest that acupuncture can be used in order to reduce symptoms and to improve sleep to some extent in patients with depression, but does not seem to have beneficial effects for patients with schizophrenia.

In **Chapter 6**, besides the question whether acupuncture is able to improve mood in patients with long-term depression or long-term schizophrenia, whether acupuncture is also able to improve cognitive functioning (working memory performance) was addressed. The patients received twelve weeks of individualized acupuncture treatment, and a pragmatic clinical trial design was used. All participants were tested twice on a mood scale and on a simple and a complex working memory task before (T1) and after (T2) acupuncture treatment. The results showed that acupuncture treatment significantly improved mood, but not working memory, in patients with depression; moreover, patients with schizophrenia seemed to have neither improved mood nor improved working memory after acupuncture treatment.

Not only is it important to establish quantitatively the group effects of acupuncture but also to look at individual patients. What effects does acupuncture have on the number and the kinds of hallucinations experienced by a patient suffering from chronic schizophrenia? In

Chapter 7, this question is investigated; moreover, sleep quality, depressive feelings, and positive and negative symptoms are further assessed. The 63-year-old woman in the case study of chapter 7 suffered from persistent hallucinations and even physical pain resulting from a hallucination of a black bird continuously pecking on her back. The patient received 12 weekly acupuncture treatments as an add-on treatment. A clinical diagnostic interview and psychological testing on sleep quality and depression were conducted before, immediately after, and 3 months after the acupuncture treatment; moreover, her psychiatrist filled in a PANSS (Positive and Negative Syndrome Scale). The results of the diagnostic interview showed that the patient experienced improved daily functioning and noticed a change in hallucinations. Although the hallucinations still occurred, she felt less disturbed by them. Interestingly, pain decreased markedly. In addition, the results showed that the overall score of the positive and the negative symptoms did not change immediately; however, a decrease in symptoms occurred three months after acupuncture treatment. Moreover, the patient described an immediate improvement in sleep; this was confirmed by her responses on a daytime sleepiness questionnaire. The patient was not able to complete a (longer) test on sleep quality beforehand, but did so after the treatment period. Also, a delayed improvement in the depression scale was found. Conclusively, the results of this case study indicate that acupuncture may be beneficial as an add-on treatment tool in patients with schizophrenia.

Previous allopathic research showed heterogeneous clinical results within the schizophrenia group and within the depression group, so the question that is investigated in **Chapter 8** is how this can be explained from a Traditional Oriental Medicine (TOM) perspective. In this study, the different TOM diagnostic patterns in patients with a Western diagnosis of schizophrenia, depression, or sleep disorders are described from a TOM literature and a clinical perspective. Psychiatric disorders can be described and treated from both a Western (allopathic) and an Eastern perspective, which is important when research on acupuncture in psychiatry is conducted. Patients with schizophrenia or with depression are likely to be undergoing Western treatment when they are referred to an acupuncturist for (add-on) treatment, so knowledge of both types of treatments is necessary to integrate them successfully. In this study, data on 30 patients with depression and 30 patients with schizophrenia are presented. It was found that if a psychiatric group, sorted in accordance with Western diagnostic principles, is diagnosed on the basis of TOM diagnostic patterns, the group can be categorized into different groups of patients with psychiatric disorders; this finding has far-reaching consequences in scientific research on acupuncture. Finally, sleep quality is discussed as a treatment objective that may play a crucial role in mediating acupuncture-induced treatment effects in patients with schizophrenia and patients with depression.

In **Chapter 9**, the clinical evidence for the use of acupuncture as an add-on treatment for patients with depression and patients with schizophrenia and the evidence on its working

mechanisms were assessed. Four databases (Medline, Scopus, ERIC, and the Cochrane Library) were searched until March 31, 2014. All systematic reviews and meta-analyses on acupuncture treatment in patients with depression and patients with schizophrenia were considered for inclusion. Randomized controlled trials (RCTs) and case studies on acupuncture and patients with schizophrenia were also included because the number of papers on the effects of acupuncture in patients with schizophrenia is very low. The primary aim of this study was to evaluate the effects of acupuncture treatment for patients with depression and patients with schizophrenia through a systematic review. The secondary aim was to evaluate possible underlying working mechanisms behind acupuncture, again through a systematic review. The results show that the overall clinical results for the use of acupuncture in treating patients with depression are promising, but only limited evidence for its effectiveness in treating patients with schizophrenia was found. Acupuncture improves the quality of life of psychiatric patients, particularly sleep quality. Brain research revealed that acupuncture has a modulating and normalizing effect on the "limbic-paralimbic-neocortical network" (LPNN), including the default mode network (DMN). Because the LPNN is related to sleep as well as emotions, this can explain why life quality and sleep are improved after acupuncture treatment.

To conclude, stronger indications were found for acupuncture's effectiveness in patients with long-term depression than for its effectiveness in patients with schizophrenia, in which only some positive effects on sleep were found. In patients with depression, acupuncture helps to improve their mood, and this might work through a positive effect via sleep. Future research on the working mechanisms of acupuncture in the treatment of patients with depression would be helpful in order to identify the processes through which acupuncture acts and to answer the question why patients with schizophrenia are seemingly less sensitive to this therapy. Possibly, acupuncture may have more effects in patients with schizophrenia that show a psychopathology more severe than those shown by the patients in the studies reported in the current thesis. Specifically, research comparing the effects of acupuncture treatment on patients with a first episode of schizophrenia to its effects on patients with chronic schizophrenia is warranted.

Deutsche Zusammenfassung

In den letzten zwanzig Jahren wird Akupunktur immer häufiger als eine alternative zusätzliche Behandlungsmethode in der Westlichen Medizin eingesetzt. Akupunktur wird besonders in der Therapie von Depressionen und seit kurzem auch bei Patienten mit Schizophrenien angewendet. Allerdings gibt es nur wenig solide wissenschaftliche Forschung nach der Effektivität von Akupunktur in der Behandlung von Patienten mit chronischen Depressionen und chronischen Schizophrenien. Die Forschungsfrage dieser Doktorarbeit ist deswegen, ob Akupunktur erfolgreich als zusätzliche Behandlungsmethode bei der Behandlung von Patienten mit chronischer Depression/Schizophrenie eingesetzt werden kann. Bevor die mögliche Effektivität einer neuen Behandlung geprüft werden kann, ist es allerdings wichtig, einen umfassenden Einblick in die Problematik der Patientengruppen zu erhalten, die untersucht werden: Patienten mit Schizophrenie und Patienten mit einer Depression. Viele Patienten leiden lange an einer Depression oder Schizophrenie und können deshalb als chronisch krank bezeichnet werden. Eine Störung wird als chronisch bezeichnet, wenn der Patient mindestens 5 Jahre an der Störung leidet. Im **ersten Kapitel** wird eine Übersicht der diagnostischen Kriterien von Schizophrenie und Depression vorgestellt. Innerhalb der Gruppe chronisch schizophrener Patienten als auch innerhalb der chronischen Depressionsgruppe unterscheiden Patienten sich oft in Merkmalen und Symptomen. Verschiedene Studien zeigten unterschiedliche Resultate für Schizophrenie, die durch die Heterogenität dieser Patientengruppe erklärt werden könnten. Auch für Depression wurde das gleiche Problem der klinischen Heterogenität gefunden. Das Maß an Chronizität könnte für die wechselnden Resultate unterschiedlicher Studien verantwortlich sein, weil Patienten sich während der ersten 5 Jahre nach der Diagnose einer psychiatrischen Störung vielleicht anders fühlen und verhalten, als in den darauffolgenden Jahren. In vielen Studien wird nicht vermerkt, wie lange die Patienten schon an einer Krankheit leiden, außerdem werden auch gemischte Gruppen untersucht. Ein weiterer wichtiger Aspekt, der unsere Aufmerksamkeit verdient und der unter anderem teilweise die festgestellte Heterogenität innerhalb der Schizophrenie-Gruppe und innerhalb der Depressionsgruppe erklären könnte, ist der vielfache Beleg für eine Korrelation zwischen psychiatrischen Störungen und Schlafstörungen. Frühere Forschung hat diese These unterstützt, indem sie gezeigt hat, dass unbehandelte Schlafstörungen das Risiko für die Entwicklung von psychiatrischen Störungen verstärken. Neben der Beschreibung der Probleme heterogener Gruppen und der Beschreibung spezifischer Patientengruppen, ist das Ziel dieser Doktorarbeit vor allem zu erforschen, ob Akupunktur als zusätzliche klinische Intervention für die Behandlung chronisch depressiver oder chronisch schizophrener Patienten eingesetzt werden kann.

Im **zweiten Kapitel** wird eine Studie präsentiert, in der untersucht wird, ob die lange Dauer der Krankheit der Patienten mit Depression und Schizophrenie die Art, wie diese Patienten selbst ihre Psychopathologie und Persönlichkeit mithilfe des MMPI-2 (Minnesota Multiphasic

Personality Inventory-2), einer Persönlichkeitsliste, bewerten, beeinflusst. Auch war die Frage, ob Demoralisierung 'assoziiert mit der langen Dauer der Krankheit' die Skalen des Persönlichkeitsfragebogens beeinflusst. Die Patienten mit chronischer Schizophrenie, die Patienten mit chronischer Depression und die gesunden Versuchspersonen füllten den MMPI-2 aus und wurden auf den Klinischen Skalen (auf English „Clinical Scales“) und auf den RC-Skalen (auf Englisch „Restructured Clinical Scales“) miteinander verglichen. Die Demoralisierung war höher bei Patienten mit Depression als bei Patienten mit Schizophrenie und beide psychiatrischen Gruppen unterschieden sich von der Gruppe gesunder Versuchspersonen. Daraus folgt, dass Patienten mit einer chronischen Depression ein vermindertes Funktionieren und eine hohe Demoralisierung zeigen, während Patienten mit chronischer Schizophrenie überraschenderweise ein fast normales Funktionieren und weniger Demoralisierung zeigen. Letzteres hat ernsthafte Konsequenzen für die Möglichkeit mit Hilfe von Akupunktur den Zustand der chronisch schizophrenen Patienten zu verbessern. Außerdem führt dieses Ergebnis zu verschiedenen Fragen in Bezug auf den MMPI-2, wobei eine ernsthaft gestörte Patientengruppe laut diesem Persönlichkeitsfragebogen ein fast normales Funktionieren zeigt. Zu diesem Thema ist daher mehr Forschung erwünscht.

Im **dritten Kapitel** richten wir uns auf einen anderen Aspekt, der die Aufmerksamkeit verdient, nämlich die Frage, ob unsere psychiatrischen Gruppen, wie so oft in der Fachliteratur berichtet, tatsächlich an Schlafstörungen leiden; und falls dies der Fall ist, an was für einer Art von Schlafstörungen leiden sie? In dieser Studie wird die subjektive Erfahrung von Parasomnien und anderen nächtlichen Verhaltensweisen bei Depression und Schizophrenie mit Hilfe eines Parasomnie Screening Fragebogens untersucht. Insgesamt wurden 21 Parasomnien und andere nächtliche Verhaltensweisen untersucht. Die Resultate zeigen, dass, obwohl alle Patienten mit Depression nächtliche Parasomnien erfahren hatten, keiner der Patienten zuvor eine Parasomnie Diagnose bekommen hatte oder deswegen behandelt worden war. 97.6% aller Versuchspersonen gaben an, nächtliche Parasomnien erfahren zu haben. Dies war am stärksten ausgeprägt bei Depression, was nach mehr klinischem Bewusstsein und besseren zukünftigen Behandlungen und Resultaten verlangt. Ein Forschungsinstrument, wie der Parasomnie Screening Fragebogen, ist essentiell, um die Patienten herauszufiltern, die an Parasomnien leiden. Es ist außerdem wichtig, sich bewusst zu sein, dass sowohl Patienten mit Schizophrenie als auch gesunde Versuchspersonen ebenfalls an Parasomnien leiden. Kurz zusammengefasst zeigt dieser Studie deutlich, dass beide Patientengruppen an Schlafstörungen leiden. Dieses Resultat zeigt, dass Schlafstörungen eine wichtige Problematik sind, die berücksichtigt werden muss, wenn neue Behandlungsformen für Patienten mit chronischer Schizophrenie und für Patienten mit Depression entwickelt und getestet werden.

Nachdem diese Einsichten in unseren chronisch psychiatrischen Patientengruppen erworben waren, wird eine der Hauptfragen in dieser Doktorarbeit erforscht. Akupunktur, eine Traditionelle Chinesische Medizin-Technik, wird als eine zusätzliche Behandlung (neben der

Standard-Westlichen medizinischen Behandlung) von Patienten eingesetzt, die an chronischer Schizophrenie oder Depression leiden. **Kapitel 4** beschreibt eine erste klinische Pilotstudie, worin untersucht wird, ob Akupunktur einen positiven Einfluss auf den Schlaf von Patienten mit Schizophrenie und Depression hat. Wie in **Kapitel 3** schon besprochen, leiden diese Patientengruppen an Schlafstörungen. Alle Versuchspersonen wurden gebeten, vor und nach einer experimentellen Kondition (wöchentliche Behandlung mit Akupunktur in einem Zeitraum von drei Monaten) oder einer Kontroll-Kondition (Warteliste) das Pittsburgh Schlaf Qualität Inventar auszufüllen. Es wurde festgestellt, dass beide Akupunktur Gruppen nach der Behandlung signifikant niedrigere Werte auf dem Fragebogen zeigten, was bei der Wartelistekondition nicht der Fall war. Außerdem zeigte sich, dass die Effektivität der Akupunktur Behandlung für die Patienten mit Schizophrenie höher war als für die Patienten mit Depression. Kurz zusammengefasst zeigt diese Studie, dass Akupunktur den Schlaf in dieser Stichprobe, die von chronisch psychiatrischen Problemen gekennzeichnet wird, zu verbessern scheint und es wird suggeriert, dass Akupunktur vielleicht eine geeignete und kosteneffektive zusätzliche (neben der Standard westlichen) Behandlung für diese Gruppe sein könnte, vor allem wenn Akupunktur in Gruppen angewendet wird.

In **Kapitel 5** wird der mögliche klinische Effekt von Akupunktur auf Schlaf weiter untersucht. Diese Studie beschreibt nochmals eine klinische Pilotstudie, worin untersucht wird, ob Akupunktur einen positiven Einfluss auf den Schlaf und die Symptome von Patienten mit Schizophrenie und von Patienten mit Depression hat. Diesmal wurden alle Versuchspersonen gebeten, in einem Zeitraum von zwei Wochen täglich ein Schlaftagebuch auszufüllen, außerdem wurden sie gebeten, einen Stimmungsfragebogen auszufüllen und die behandelnden Psychiater wurde gebeten, eine Liste auszufüllen in Bezug auf die positiven und negativen Symptome der Patienten mit Schizophrenie. Danach wurden sie nach dem Zufallsprinzip einer drei Monate dauernden (wöchentlichen) experimentellen Akupunktur Kondition oder einer Warteliste Kondition zugeteilt. Nach drei Monaten wurden alle Tests wiederholt. Patienten mit Depression schliefen kürzer und fühlten sich erschöpfter im Vergleich zu den Patienten mit Schizophrenie. Außerdem waren sie im Vergleich zu den gesunden Versuchspersonen während der Nacht länger wach, brauchten mehr Zeit um einzuschlafen, beurteilten ihren Schlaf als weniger erholsam, fühlten sich erschöpfter und hatten sie ein niedrigeres durchschnittliches Leistungsvermögen, während die Patienten mit Schizophrenie im Vergleich zu den gesunden Versuchspersonen lediglich ein niedrigeres durchschnittliches Leistungsvermögen berichteten. Außerdem wurde festgestellt, dass Akupunktur den Schlaf und die depressiven Symptome von Patienten mit Depression leicht verbesserte, aber den Schlaf und die positiven und negativen Symptome von Patienten mit Schizophrenie nicht beeinflusste. Diese vorläufigen Resultate suggerieren, dass Akupunktur gebraucht werden kann, um die Symptome von Patienten mit Depression teilweise zu vermindern und den Schlaf von Patienten mit Depression zu verbessern, aber Akupunktur scheint keinen nennenswerten Effekt bei Patienten mit Schizophrenie zu haben.

In **Kapitel 6** wird, neben der Frage ob Akupunktur die Stimmung von Patienten mit chronischer Depression oder Schizophrenie verbessern kann, die Frage gestellt, ob Akupunktur auch kognitives Funktionieren (die Arbeitsgedächtnis-Leistung) von Patienten mit chronischer Depression und Schizophrenie verbessern kann. Die Patienten bekamen in einem Zeitraum von zwölf Wochen eine individuelle Akupunktur Behandlung und in der Studie wurde von einem pragmatischen, klinischen, Studie-Design gebrauch gemacht. Alle Versuchspersonen wurden sowohl vor (T1) als auch nach der Akupunktur Behandlung (T2) mit Hilfe einer Stimmungsliste und einer einfachen und einer komplizierten Arbeitsgedächtnis-Aufgabe getestet. Die Resultate zeigen, dass die Akupunktur Behandlung zwar die Stimmung, aber nicht das Arbeitsgedächtnis der Patienten mit Depression signifikant verbessert. Die Stimmung und das Arbeitsgedächtnis von Patienten mit Schizophrenie verbesserten sich nicht nach der Akupunktur Behandlung.

Es ist nicht nur wichtig, die quantitativen Effekte von Akupunktur auf Gruppeniveau zu untersuchen, sondern auch die Wirkung auf individuellem Niveau zu betrachten. Was sind zum Beispiel die Effekte von Akupunktur auf (die Zahl und die Art) der Halluzinationen eines Patienten mit chronischer Schizophrenie? In **Kapitel 7** wird diese Frage näher untersucht und außerdem werden die Qualität des Schlafs, die depressiven Gefühle und die positiven und negativen Symptome des Patienten erforscht. Es handelt sich bei dem Kasus um eine 63 jährige Frau, die an persistierenden Halluzinationen und sogar an physischen Schmerzen leidet, die durch Halluzination einer Krähe hervorgerufen werden, die immer wieder in ihren Rücken pickt. Die Patientin wurde während 12 Wochen zusätzlich (neben der Standard Westlicher) mit Akupunktur behandelt. Ein klinisches, diagnostisches Interview wurde bei ihr durchgeführt und sie wurde psychologisch getestet (auf die Qualität des Schlafs und auf Depression), auch wurden ihre positiven und negativen Symptome von ihrem Psychiater mittels des PANSS (auf Englisch „Positive and Negative Syndrome Scale“) eingeschätzt. Dies fand sowohl direkt vor und direkt nach der 12 wöchentlichen Akupunktur Behandlung statt, als auch drei Monate, nachdem die Akupunktur Behandlung abgeschlossen war. Die Ergebnisse des diagnostischen Interviews zeigen, dass die Patientin ein verbessertes Funktionieren während des Tages erfuhr und sie beobachtete eine Veränderung ihrer Halluzinationen. Sie hatte zwar noch immer Halluzinationen, aber sie fühlte sich dadurch weniger belastet. Interessant war auch, dass der Schmerz der Patientin beträchtlich weniger wurde. Außerdem zeigten die Resultate, dass sich der gesamt Score der positiven und der negativen Symptome direkt nach der Akupunktur Behandlung zwar nicht änderte, aber drei Monate nach Abschluss der Akupunktur Behandlung eine Verminderung der Symptome stattfand. Auch gab die Patientin an, eine sofortige Verbesserung des Schlafs zu spüren, was auch vom Schlaffragebogen bestätigt wurde. Die Patientin war vor der Akupunktur Behandlung nicht in der Lage, einen längeren Schlafqualitätsfragebogen auszufüllen, aber nach der Behandlungsperiode war sie wohl dazu in der Lage. Auch wurde eine Verbesserung auf der Depressionsskala gefunden, die sich zwar nicht direkt nach der Behandlung, aber drei Monate nach Abschluss der Behandlung zeigte. Es wird daraus geschlossen, dass die

Resultate dieser Fallstudie zeigen, dass Akupunktur einen positiven Effekt bei Patienten mit Schizophrenie haben könnte, wenn sie als zusätzliche Behandlung (neben der Westlichen Behandlung) eingesetzt wird.

In früheren Westlichen Studien wurden heterogene klinische Resultate innerhalb der Schizophrenie Gruppe und innerhalb der Depressionsgruppe gefunden. In **Kapitel 8** wird untersucht, wie diese Heterogenität aus der Traditionellen Östlichen Medizinischen Perspektive erklärt werden könnte. In dieser Studie werden die unterschiedlichen Traditionellen Östlichen Medizinischen (diagnostischen) Muster bei Patienten beschrieben, die eine Westliche Diagnose der Schizophrenie, oder eine Diagnose der Depression, oder eine Diagnose der Schlafstörung haben. Diese Verhaltensmuster werden sowohl aus der Perspektive der Fachliteratur, als auch aus der klinischen Perspektive beschrieben. Psychiatrische Störungen können sowohl aus Westlicher, als auch aus Östlicher Perspektive beschrieben und behandelt werden, was wichtig ist, wenn man nach der Wirkung von Akupunktur in der Psychiatrie forscht. Patienten mit Schizophrenie und Patienten mit Depression stehen nämlich höchstwahrscheinlich unter Westlicher Behandlung, wenn sie zu einem Akupunkteur oder einer Akupunkteurin für eine (zusätzliche) Behandlung überwiesen werden. Deswegen sind Kenntnisse beider Behandlungsmethoden dringend erforderlich, um eine erfolgreiche Integration zu ermöglichen. In dieser Studie werden die Daten von 30 Patienten mit Depression und 30 Patienten mit Schizophrenie präsentiert. Es wurde festgestellt, dass wenn eine psychiatrische Gruppe, diagnostiziert konform der Westlichen diagnostischen Kriterien, auf Grund von Traditionell Östlichen (diagnostischen) Mustern diagnostiziert wird, die gleiche psychiatrische Gruppe in verschiedenen Gruppen von Patienten mit psychiatrischen Störungen kategorisiert werden kann. Diese Erkenntnis hat weitreichende Konsequenzen für die wissenschaftliche Forschung mit Akupunktur. Schließlich wird die Schlafqualität als Behandlungsziel besprochen, die eine entscheidende, beeinflussende Rolle für die durch Akupunktur induzierten Behandlungseffekte bei Patienten mit Schizophrenie und bei Patienten mit Depression spielen könnte.

In **Kapitel 9** werden sowohl der klinische Beleg für den Gebrauch von Akupunktur als zusätzliche Behandlung bei Patienten mit Depression und Schizophrenie, als auch der Beleg für die zugrundeliegenden Wirkungsmechanismen näher betrachtet. Dafür werden vier Karteien (Medline, Scopus, ERIC, und Cochrane Library) bis zum 31. März, 2014 durchsucht. Diese Studie umfasst alle systematischen Review Studien und Meta-Analysen im Bereich der Akupunktur Behandlung von Depression und Schizophrenie. Randomisierte, kontrollierte Studien und Fallstudien im Bereich der Akupunktur und Schizophrenie wurden auch mit eingeschlossen, weil die Anzahl der Studien, in denen Akupunktur bei Patienten mit Schizophrenie erforscht wird, sehr klein ist. Das Hauptziel dieser Studie war das Bewerten der Behandlungseffekte von Akupunktur bei Depression und Schizophrenie mittels eines systematischen Reviews. Das zweite Ziel war das Bewerten möglicher, zugrundeliegender Wirkungsmechanismen der Akupunktur, ebenfalls mit Hilfe eines systematischen Reviews.

Die allgemeinen Resultate für den Gebrauch von Akupunktur bei Depression sind vielversprechend, aber die Effektivität von Akupunktur bei Schizophrenie konnte nur wenig belegt werden. Akupunktur verbessert die Lebensqualität von psychiatrischen Patienten und vor allem die Schlafqualität. Hirnforschung hat gezeigt, dass Akupunktur einen modulierenden und normalisierenden Effekt auf das “Limbische-Paralimbische-Neocorticale Netzwerk” und das „Default-Mode Netzwerk“ hat. Weil das “Limbische-Paralimbische-Neokorticale Netzwerk“ sowohl mit Schlaf als auch mit Emotionen in Verbindung gesetzt wird, kann dieses Netzwerk die Verbesserung der Lebensqualität und des Schlafs nach Akupunktur erklären.

Abschließend kann der Schluss gezogen werden, dass es stärkere Indizien für die Effektivität von Akupunktur in der Behandlung von Patienten mit Depression gibt, als in der Behandlung von Patienten mit Schizophrenie, wo lediglich kleine Effekte auf Schlaf gefunden wurden. Bei Patienten mit Depression scheint Akupunktur die Stimmung zu verbessern und dies könnte sich positiv auf den Schlaf auswirken. Zukünftige Forschung nach den Wirkmechanismen von Akupunktur bei Patienten mit Depression ist nützlich um zu sehen, welche Prozesse der Akupunktur zugrunde liegen und um die Frage zu beantworten, warum Patienten mit Schizophrenie offensichtlich weniger sensibel auf die Therapie reagieren. Möglicherweise hat Akupunktur mehr Effekte bei schizophrenen Patienten, die ernsthaftere psychopathologische Symptome zeigen, als die Patienten, die in den hiesigen Studien aufgenommen wurden. Vor allem Forschung, die ersterkrankte Patienten mit Schizophrenie und Patienten mit chronischer Schizophrenie in der Behandlung mit Akupunktur miteinander vergleicht, ist indiziert.

Nederlandse Samenvatting

Gedurende de laatste twee decennia is het gebruik van acupunctuur als een alternatieve extra behandeltechniek in de Westerse geneeskunde aan het toenemen. Acupunctuur wordt vooral gebruikt als een therapie voor depressie en recent zijn clinici ook gestart om het als een extra behandeling van schizofrenie in te zetten. Echter, solide wetenschappelijk onderzoek naar de effectiviteit van acupunctuur in de behandeling van patiënten met depressie en schizofrenie is schaars, omdat in het bijzonder de werkzaamheid in de behandeling van chronische stoornissen compleet ontbreekt. De onderzoeksvraag van het huidige proefschrift is daarom of acupunctuur succesvol kan worden gebruikt als een extra behandeltechniek in de behandeling van chronische patiënten met depressie en in de behandeling van chronische patiënten met schizofrenie. Echter, voordat de mogelijke effectiviteit van een nieuwe behandeling kan worden getest, is het belangrijk om een goed inzicht te verkrijgen in de problematiek van de patiënten groepen die worden onderzocht: patiënten met schizofrenie en depressie. Veel patiënten lijden lang aan depressie of schizofrenie en daarom kunnen deze worden getypeerd als chronisch. Een stoornis wordt chronisch genoemd, wanneer de patiënt minstens 5 jaar aan die stoornis lijdt. In **Hoofdstuk 1** wordt een overzicht van de diagnostische criteria van schizofrenie en depressie gegeven. Binnen de chronische schizofrenie groep evenals binnen de chronische depressie groep verschillen patiënten vaak in kenmerken en symptomen. In verscheidende studies werden uiteenlopende resultaten voor schizofrenie gevonden; deze resultaten zouden wellicht kunnen worden verklaard door de heterogeniteit van de desbetreffende patiënten groep. Echter, voor depressie werd hetzelfde probleem van klinische heterogeniteit gevonden. De mate van chroniciteit zou verantwoordelijk kunnen zijn voor de wisselende resultaten tussen studies, omdat patiënten wellicht anders functioneren en zich anders voelen gedurende de eerste 5 jaar nadat ze zijn gediagnosticeerd met een psychiatrische stoornis, dan in de jaren die daarop volgen. In vele studies wordt niet genoemd hoe lang de patiënten al aan een ziekte leden en ook worden gemengde groepen gebruikt. Een ander belangrijk aspect dat onze aandacht verdient en dat mede de gevonden heterogeniteit binnen de schizofrenie en depressie groep zou kunnen verklaren, is dat er veel bewijs is voor een correlatie tussen psychiatrische stoornissen en slaap stoornissen. Dit wordt verder ondersteund door het feit dat eerder onderzoek heeft aangetoond dat wanneer slaapstoornissen niet behandeld worden, het risico voor het ontwikkelen van psychiatrische stoornissen toeneemt. Naast het in kaart brengen van de problemen achter de heterogene groepen en naast de beschrijving van de specifieke patiëntengroepen, is het doel van dit proefschrift bovenal, te onderzoeken of acupunctuur kan worden toegepast als extra klinische interventie bij de behandeling van patiënten, die lijden aan chronische schizofrenie of depressie en slaap stoornissen.

In **Hoofdstuk 2** wordt een studie gepresenteerd waarin wordt onderzocht of de lange duur van de ziekte van de depressie en schizofrenie patiënten de manier waarop deze patiënten zelf hun psychopathologie en persoonlijkheid op de MMPI-2 (Minnesota Multiphasic

Personality Inventory-2), een persoonlijkheidsvragenlijst weergeven, beïnvloedt. Verder was het de vraag of demoralisatie, hetgeen kan worden omschreven als een reactie dat op de chroniciteit van de stoornis kan volgen, de schalen van de persoonlijkheidsvragenlijst beïnvloedt. De chronische patiënten met schizofrenie, de chronische patiënten met depressie en de gezonde proefpersonen vulden hiervoor de MMPI-2 in en werden op de Klinische Schalen (Clinical Scales) en op de Geherstructureerde Klinische (Restructured Clinical) Schalen vergeleken. Demoralisatie was hoger bij de patiënten met depressie dan bij de patiënten met schizofrenie en beide psychiatrische groepen verschilden van de groep met gezonde proefpersonen. Er wordt geconcludeerd dat patiënten met een chronische depressie een verminderd functioneren en een hoge demoralisatie laten zien, terwijl patiënten met chronische schizofrenie verrassend genoeg een bijna normaal functioneren laten zien en minder demoralisatie. Dit laatste zou ernstige consequenties kunnen hebben voor de mogelijkheid voor acupunctuur om de toestand in de chronische schizofrenie groep te verbeteren. Bovendien geeft dit resultaat aanleiding tot verschillende vragen met betrekking tot de MMPI-2, omdat een ernstig gestoorde patiëntengroep (bijna) normaal scoort op deze persoonlijkheidsvragenlijst, vraagt dit duidelijk om nader onderzoek.

In **Hoofdstuk 3**, komt een ander aspect dat de aandacht verdient aan bod, namelijk de vraag of onze psychiatrische groepen inderdaad aan slaap stoornissen lijden, zoals vaak in de literatuur wordt gerapporteerd en mocht dit het geval zijn; aan wat voor een soort slaap stoornissen lijden ze dan? In deze studie wordt de subjectieve ervaring van parasomnieën en andere nachtelijke gedragingen in depressie en schizofrenie onderzocht met behulp van een parasomnie screening lijst. In totaal werden 21 parasomnieën en andere nachtelijke gedragingen onderzocht. Er werd gevonden, dat hoewel alle depressie patiënten nachtelijke gedragingen hadden ervaren, geen van de patiënten een eerdere parasomnie diagnose had gekregen of hiervoor was behandeld. 97.6% van alle proefpersonen gaven aan dat ze nachtelijke gedragingen ervaren hadden. Dit bleek het hoogst bij depressie, hetgeen om meer klinisch besef vraagt en om betere toekomstige behandelingen en resultaten. Een onderzoeksinstrument, zoals een parasomnie screening lijst is essentieel in het er uit filteren van patiënten, die last van parasomnieën lijken te hebben. Desalniettemin is het belangrijk om te beseffen dat zowel schizofrenie patiënten als gezonde proefpersonen ook aan parasomnieën lijden. Kort samengevat, laat deze studie duidelijk zien dat beide patiëntengroepen aan slaapstoornissen lijden. Dit resultaat geeft aan dat slaapstoornissen een belangrijke problematiek zijn, waarmee rekening moet worden gehouden wanneer nieuwe behandelingsvormen voor chronische schizofrenie en depressie patiënten worden ontwikkeld en getest.

Na deze inzichten in onze chronische psychiatrische patiëntengroepen te hebben verkregen, wordt vervolgens een van de hoofdvragen van de thesis onderzocht. Acupunctuur, een Traditionele Chinese Geneeskunde techniek, wordt als een extra behandeling (naast de standaard Westerse geneeskunde behandeling) ingezet bij de behandeling van patiënten die

lijden aan chronische schizofrenie en depressie. **Hoofdstuk 4** beschrijft een eerste klinische pilotstudie, waarin wordt onderzocht of acupunctuur een positieve invloed op de slaap van patiënten met schizofrenie en depressie heeft. Zoals in **Hoofdstuk 3** werd besproken, lijdt deze patiëntengroep aan slaapstoornissen. Alle proefpersonen werd gevraagd de Pittsburgh Slaap Kwaliteits Vragenlijst in te vullen voor en na de experimentele (drie maanden wekelijkse acupunctuur behandeling) of controle (wachtlijst) conditie. Er werd gevonden, dat beide acupunctuur groepen significant lagere scores op de slaapvragenlijst lieten zien, wat niet het geval was voor de wachtlijstconditie. Bovendien werd gevonden dat de effectiviteit van de acupunctuurbehandeling voor de schizofrenie patiënten hoger was dan voor de depressie patiënten. Kort samengevat, laat deze studie zien, dat acupunctuur in staat lijkt te zijn de slaap in deze steekproef, die gekenmerkt wordt door chronische psychiatrische problemen, te verbeteren en wordt gesuggereerd dat acupunctuur wellicht een geschikte en kosteneffectieve extra (naast hun standaard Westerse) behandeling voor deze groep zou kunnen zijn, vooral als acupunctuur groepsgewijs wordt toegepast.

In **Hoofdstuk 5** wordt het mogelijke klinische effect van acupunctuur op slaap verder onderzocht. Deze studie beschrijft opnieuw een eerste klinische, pilotstudie waarin wordt onderzocht of acupunctuur een positieve invloed op de slaap en de symptomen van schizofrenie en depressie patiënten heeft. Dit keer werden alle proefpersonen gevraagd gedurende twee weken een slaapdagboek bij te houden, daarnaast werd gevraagd of ze een stemmingsvragenlijst in konden vullen en aan de behandelende psychiaters werd gevraagd om een lijst in te vullen betreffende positieve en negatieve symptomen van de patiënten met schizofrenie. Daarna werden zij at random toebedeeld aan een drie maanden durende (wekelijkse) experimentele acupunctuur conditie, of aan een wachtlijst conditie. Na de drie maanden werden alle testen herhaald. Patiënten met depressie sliepen korter en voelden zich meer uitgeput in vergelijking tot de patiënten met schizofrenie. Bovendien waren zij in vergelijking tot de gezonde proefpersonen langer wakker gedurende de nacht, hadden zij meer tijd nodig om in slaap te vallen, beoordeelden ze hun slaap als minder ontspannen, voelden zij zich meer uitgeput en hadden zij een lager gemiddeld prestatievermogen, terwijl de schizofrenie patiënten enkel een lager gemiddeld prestatievermogen rapporteerden in vergelijking tot de gezonde proefpersonen. Daarnaast werd gevonden dat acupunctuur slaap en depressieve symptomen van patiënten met depressie licht verbeterde, maar de slaap en de positieve en negatieve symptomen van de patiënten met schizofrenie niet beïnvloedde. Deze voorlopige resultaten suggereren dat acupunctuur kan worden gebruikt om tot op zekere hoogte de symptomen te verminderen en slaap te verbeteren in patiënten met een depressie, maar acupunctuur lijkt geen noemenswaardig effect te hebben voor patiënten met schizofrenie.

In **Hoofdstuk 6** wordt, naast de vraag of acupunctuur in staat is de stemming van chronische depressie en schizofrenie patiënten te verbeteren, de vraag gesteld of acupunctuur ook het cognitief functioneren (de werkgeheugen prestatie) van chronische depressie en

schizofrenie patiënten kan verbeteren. De patiënten kregen twaalf weken een individuele acupunctuurbehandeling en in het onderzoek werd gebruik gemaakt van een pragmatisch, klinisch, studiedesign. Alle proefpersonen werden twee keer op een stemmingsschaal, een simpele en een complexe werkgeheugentaak getest, een keer voor (T1) en een keer na de acupunctuurbehandeling (T2). De resultaten tonen aan dat de acupunctuurbehandeling wel de stemming, maar niet het werkgeheugen van de depressie patiënten significant verbetert. Verder bleken de stemming en het werkgeheugen van de schizofrenie patiënten niet te verbeteren na de acupunctuurbehandeling.

Het is niet alleen belangrijk om naar de kwantitatieve effecten van acupunctuur op groepsniveau te kijken, maar ook naar de uitwerking ervan op individueel niveau. Wat zijn bijvoorbeeld de effecten van acupunctuur op (het aantal en het soort) hallucinaties van een patiënt met chronische schizofrenie? In **Hoofdstuk 7**, wordt deze vraag nader onderzocht en daarnaast worden de kwaliteit van de slaap, de depressieve gevoelens en de positieve en negatieve symptomen van de patiënt in kaart gebracht. De casus gaat over een 63 jarige vrouw, die aan persistente hallucinaties lijdt en zelfs last van fysieke pijn heeft, als gevolg van de hallucinatie van een kraai, die alsmaar in haar rug blijft pikken. De patiënte kreeg gedurende 12 weken een acupunctuurbehandeling als extra (naast de standaard Westerse) behandeling. Een klinisch, diagnostisch interview werd bij haar afgenomen en ze werd psychologisch getest (op de kwaliteit van de slaap en op depressie) daarnaast werden de positieve en negatieve symptomen door haar psychiater ingeschat middels de PANSS (Positive and Negative Syndrome Scale). Dit vond zowel direct voor, direct na de 12 weken acupunctuurbehandeling, als ook 3 maanden na het beëindigen van de acupunctuurbehandeling plaats. Uit de resultaten van het diagnostisch interview bleek dat de patiënte een verbeterd functioneren gedurende de dag ervoer en ze merkte een verandering in haar hallucinaties op. Hoewel ze nog steeds hallucinaties had, voelde ze zich daar minder door belast. Interessant was ook dat haar pijn aanzienlijk verminderde. Bovendien lieten de resultaten zien, dat de totale score van de positieve en de negatieve symptomen onmiddellijk na de acupunctuurbehandeling niet veranderde, echter 3 maanden na het beëindigen van de acupunctuurbehandeling vond er een vermindering in van de symptomen plaats. Ook beschreef de patiënte een onmiddellijke verbetering van de slaap, wat verder bevestigd werd door een slaperigheidsvragenlijst. De patiënte was niet in staat om vooraf aan de acupunctuurbehandeling een langere slaapkwaliteitsvragenlijst in te vullen, maar was hiertoe wel in staat na de behandelperiode. Ook werd een verbetering op de depressie schaal gevonden eveneens niet direct, maar 3 maanden na het beëindigen van de behandeling. Er wordt geconcludeerd, dat de resultaten van deze casusstudie aangeven, dat acupunctuur een positief effect zou kunnen hebben bij patiënten met schizofrenie wanneer het als een extra behandeling (naast de standaard Westerse) wordt ingezet.

In eerder Westers onderzoek werden heterogene klinische resultaten binnen de schizofrenie groep en binnen de depressie groep gevonden. In **Hoofdstuk 8** wordt onderzocht hoe deze

heterogeniteit vanuit een Traditioneel Oosters Geneeskundig perspectief verklaard zou kunnen worden. In deze studie worden de verschillende Traditioneel Oosterse Geneeskunde (diagnostische) patronen beschreven bij patiënten, die een Westerse diagnose schizofrenie, of een diagnose depressie, of een diagnose slaapstoornissen hebben en dit wordt zowel vanuit een TOM literatuur- als vanuit een klinisch perspectief gedaan. Psychiatrische stoornissen kunnen zowel vanuit een Westers als vanuit een Oosters perspectief worden beschreven en behandeld, wat van belang is wanneer onderzoek naar acupunctuur in de psychiatrie wordt gedaan. Patiënten met schizofrenie en patiënten met depressie staan namelijk (hoogst)waarschijnlijk onder Westerse behandeling wanneer zij naar een acupuncturist(e) voor een (extra) behandeling worden door verwezen en zodoende is kennis van beide behandelmethoden noodzakelijk om tot een succesvolle integratie te kunnen komen. In deze studie wordt de data van 30 patiënten met depressie en 30 patiënten met schizofrenie gepresenteerd. Er werd gevonden, dat als een psychiatrische groep, ingedeeld in overeenstemming met de Westerse diagnostische criteria, wordt gediagnosticeerd op basis van de Traditioneel Oosterse (diagnostische) patronen, diezelfde psychiatrische groep kan worden gecategoriseerd in verschillende groepen van patiënten met psychiatrische stoornissen. Deze bevinding heeft verregaande consequenties voor het wetenschappelijk onderzoek naar acupunctuur. Ten slotte wordt slaapkwaliteit als een behandeldoel besproken, dat een cruciale, mediërende rol zou kunnen spelen bij de acupunctuur geïnduceerde behandeleffecten die bij schizofrenie en depressie patiënten worden gevonden.

In **Hoofdstuk 9**, worden het klinisch bewijs voor het gebruik van acupunctuur als extra behandeling bij patiënten met depressie en schizofrenie en het bewijs voor de onderliggende werkmechanismen nader onderzocht. Hiervoor werden vier databases (Medline, Scopus, ERIC, en de Cochrane Library) tot 31 maart, 2014 doorzocht. In deze studie werden alle systematische review studies en meta-analyses op het gebied van acupunctuurbehandeling bij depressie en schizofrenie geïncludeerd. Gerandomiseerde, gecontroleerde studies en casus studies op het gebied van acupunctuur en schizofrenie werden ook geïncludeerd, omdat het aantal studies naar acupunctuur in de behandeling van patiënten met schizofrenie nogal klein is. Het hoofddoel van deze studie was het evalueren van de behandeleffecten van acupunctuur bij depressie en schizofrenie door middel van systematische review. Het tweede doel was het evalueren van mogelijke, onderliggende werkmechanismen achter acupunctuur, eveneens door middel van systematische review. De algehele resultaten voor het gebruik van acupunctuur bij depressie zijn veel belovend, echter slechts beperkt bewijs werd gevonden voor de effectiviteit van acupunctuur bij schizofrenie. Acupunctuur verbetert de levenskwaliteit van psychiatrische patiënten en dan vooral de slaapkwaliteit. Hersenonderzoek heeft aangetoond dat acupunctuur een modulerend en normaliserend effect heeft op het “limbisch-paralimbisch-neocorticale netwerk”, inclusief het “default-mode netwerk”. Omdat het limbisch-paralimbisch-

neocorticale netwerk zowel gerelateerd is aan slaap als emoties kan dit netwerk de verbetering in levenskwaliteit en slaap na acupunctuur verklaren.

Afsluitend kan worden geconcludeerd dat er sterkere indicaties werden gevonden voor een effectiviteit van acupunctuur in de behandeling van patiënten met depressie dan voor patiënten met schizofrenie, waarin slechts voorzichtige effecten op slaap werden gevonden. In patiënten met depressie, lijkt acupunctuur de stemming te verbeteren en dit zou kunnen werken via een positief effect op slaap. Toekomstig onderzoek naar de werkmechanismen van acupunctuur in patiënten met depressie is bruikbaar om te zien via welke processen acupunctuur werkt en om de vraag te beantwoorden waarom patiënten met schizofrenie schijnbaar minder sensitief voor deze therapie zijn. Mogelijk is het zo, dat acupunctuur meer effect heeft in patiënten met schizofrenie, die meer ernstige psychopathologie laten zien dan de patiënten in de huidige thesis. Vooral acupunctuur onderzoek dat eerste episode patiënten met schizofrenie vergelijkt met chronische patiënten vergelijkt is geindiceerd.

Curriculum Vitae

Peggy Bosch was born on the 4th of October 1977 in Blerick, the Netherlands. After finishing her secondary education at the College Marianum in Venlo in 1997, she studied psychology at the Radboud University, Nijmegen (the Netherlands), receiving her Master in Clinical Psychology in 2003. In 2002 she already started her first job as a psychologist in a forensic psychiatric department at the then called Rheinische Kliniken Bedburg-Hau. After one and a half years, she quit her job and together with her partner Maurits, she left Germany and moved to Bergen (Norway), from where Peggy, finished her acupuncture education at the Shenzhou Open University of TCM in Amsterdam, worked as a nurse and also as a research assistant, preparing her later project on acupuncture, schizophrenia and depression. Moreover, she started to study for the Heilpraktiker (alternative and complementary health care professional by German law) state exam in Germany and visited numerous conferences in psychiatry, psychology, and acupuncture. In the autumn of 2007, Peggy (and Maurits) moved back to Kleve where she started her PhD-student project at the Biological Psychology Department at the Radboud University, Nijmegen, the Netherlands, with Prof. Ton Coenen and Prof. Gilles van Luijtelaar as her promoters, gathering data during her fulltime job at the now called LVR-Klinik Bedburg-Hau (psychiatry and trauma department). Maurits and Peggy edited a book on Schizophrenia, Sleep and Acupuncture, published by Hogrefe and Huber in 2008. In 2010, Peggy passed her state exam as Heilpraktiker in Krefeld (Germany) and in 2012 and 2013 she visited trauma courses for her work at the clinic. Furthermore, she is the coordinator for apprentices in the clinic and she is the supervisor for (practical and master thesis) apprentices. Due to collaboration between the LVR-Klinik Bedburg-Hau and the Vincent van Gogh Institute in Venray, she is also a member of the local committee of scientist-practitioners (Commissie Wetenschappelijke Onderzoeksparticipatie) at the Vincent van Gogh Institute in Venray under Prof. Jos Egger, since 2013. In her spare time, she works as a psychologist at the Ambulatorium Otto Gerard Heldring Stichting in Zetten (the Netherlands), where she previously wrote psychological reports and now teaches psychodiagnostics. Since 2010, Peggy holds a position in the East West Integration WHO Department at Kyung Hee University, Seoul, Korea. Peggy is reviewer for several journals, was chair at several conferences and often functions as (keynote) speaker or lecturer. She lectured for the Deutsche Heilpraktiker Schule in Leipzig in 2013 and 2014, and since 2014 she is a lecturer for the Shenzhou Open University of TCM and for International lectures.

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Peggy

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